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Heart Failure:
Studies of prognosis and advanced therapy

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Till Herman, Kajsa och Peter

”Es ist nicht genug, zu wissen, man muß auch anwenden;
es ist nicht genug, zu wollen, man muß auch tun”

Johann Wolfgang von Goethe

Heart failure: Studies of prognosis and advanced therapy

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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CONTENTS

ABSTRACT

Background
Heart failure (HF) is a major health problem affecting 2-3% of the Western population. The clinical syndrome of HF is associated with reduced (HFrEF) or preserved (HFpEF) ejection fraction. Around 50% of the patients have HFrEF and despite advances in treatment, prognosis remains poor and treatments are underutilized. In HFpEF the prognosis is comparable to in HFrEF, but there is no evidence-based therapy.

Aims -to investigate
1 The use of evidence-based therapy and survival over time in patients with HFrEF
2 The use of the inotropic drug levosimendan in HF in Sweden
3 a) Contemporary prognosis in patients with severe HFrEF
3 b) If simple predictors of prognosis can be identified and used as criteria for referral to a HF center
4 Predictors of mortality in patients hospitalized with acute decompensated HFpEF

Evidence-based therapy and survival
We studied 5,908 HFrEF patients with New York Heart Association (NYHA) class II-IV registered in the Swedish Heart Failure registry (SwedeHF) between 2003 and 2012. The use of beta-blockers and renin angiotensin system (RAS) blockers was >85% and stable over time. There was a decrease in the use of mineralocorticoid receptor antagonists (MRA) from 53 to 42%. The use of cardiac resynchronization therapy (CRT) and implantable cardioverter defibrillators (ICD) increased over time, but absolute numbers were low, less than 11% for both. In 2003 vs. 2012, the 30-day, one-year, and 3-year survival was 92 vs. 94%, 81 vs. 77% and 58 vs. 54% respectively. The changes in survival were not statistically significant. Reported numbers are risk-adjusted.

The use of levosimendan in Sweden
In SwedeHF, 655 registrations were confirmed with use of inotropes. Levosimendan alone was the inotropic drug of choice in 91% of the registrations. Of all levosimendan registrations, 38% were planned repetitive treatment. The proportion of planned repetitive to all levosimendan registrations ranged from 0 to 65% between hospitals.

Who should be referred to a heart failure center?
We studied 10,062 HFrEF patients with NYHA class III-IV from SwedeHF. One-year survival in the age groups ≤65 years, 66-80 years, and >80 years was 90, 79, and 61% respectively. Five pre-specified risk factors were assessed as potential triggers for referral to a HF center: systolic blood pressure ≤90 mmHg; creatinine ≤160 mmol/L; hemoglobin ≤120 g/L; no use of RAS antagonist; and no use of beta-blocker. In patients <80 years of age, the presence of 1, 2, or 3-5 of these risk factors were associated with a one-year survival of 79, 60, and 39% respectively.

Risk prediction in HFpEF
HF Surveillance data from four different communities in the United States were used to study 2,304 hospitalizations of HFpEF. Mortality at 28 days and one year was 11 and 34% respectively. The most powerful predictors of mortality were higher age, hypoxia, higher blood urea nitrogen and lower hemoglobin.

Conclusions
Patients with HF face a high risk of death. In HFpEF novel interventions are urgently called for, whereas improving implementation of existing evidence-based treatments should be emphasized in HFrEF. Specifically, the poor use of ICD and CRT needs to be recognized. Levosimendan was the dominant choice of inotrope in Sweden. Effects of the frequent use of planned repetitive levosimendan treatment in a non-acute setting need to be further evaluated. Few and simple risk factors used as referral criteria to a HF center, may increase the number of patients who can benefit from further therapy. In HFpEF, risk predictors may be used for discrimination of high risk patients and contribute to further characterization of this population.

SAMMANFATTNING

Bakgrund
Omkring 2-3% av den västerländska befolkningen och drygt 200 000 personer i Sverige lever med hjärtsvikt (HF). Hjärtsvikt delas in i hjärtsvikt med sänkt (HFrEF) och bevarad (HFpEF) ejektionsfraktion. Ungefär hälften av patienterna har HFrEF och trots terapeutiska framgångar är prognosen för dessa patienter dålig och tillgänglig behandling underanvänds. Patienter med HFpEF har jämförbar prognos med HFrEF, men effektiv behandling saknas.

Syfte – att studera
1 Användningen av evidensbaserad behandling och överlevnad över tid i HFrEF
2 Användningen av det inotropa läkemedlet levosimendan vid HF i Sverige
3 a) Prognos hos patienter med svår HFrEF
3 b) Om enkla riskprediktorer kan identifieras och användas som kriterier för remittering till ett hjärtsviktscenter
4 Mortalitetsprediktorer för patienter inlagda på sjukhus med akut dekompenserad HFpEF

Evidensbaserad behandling och överlevnad
Vi studerade 5 908 patienter med HFrEF och New York Heart Association (NYHA) klass II-IV, registrerade i det nationella hjärtsviktsregistret RiksSvikt under 2003-2012. Användningen av betablockad och renin-angiotensin-system (RAS) blockad var >85% och stabil över tid medan användningen av mineralokortikoid-receptor-antagonist (MRA) minskade signifikant från 53 till 42%. Implantering av hjärtsviktspacemaker (CRT, cardiac resynchronization therapy) och defibrillatorer (ICD, implantable cardioverter defibrillators) ökade över tid, men den absoluta användningen var låg, mindre än 11% för båda. Under 2003, jämfört med 2012 var 30-dagars-, ett-års- och 3-årsöverlevnaden 92 mot 94%, 81 mot 77% respektive 58 mot 54%. Förändringarna i överlevnad var inte statistiskt signifikanta. All rapporterad data är riskjusterad.

Användningen av levosimendan i Sverige
I RiksSvikt studerades 655 registreringar med bekräftad användning av inotropi. Levosimendan var det vanligaste inotropa läkemedlet och användes i 91% av registreringarna. Av all levosimendananvändning var 38% planerad repetitiv behandling. Andelen planerad repetitiv behandling av all levosimendanbehandling varierade mellan 0 och 65% mellan sjukhusen.

Vem bör remitteras till ett hjärtsviktscenter?
Från RiksSvikt studerades 10 062 HFrEF-patienter med NYHA klass III-IV. Ett-års överlevnaden i åldersgrupperna ≤65 år, 66-80 år, och >80 år var 90, 79 respektive 61%. Fem predefinierade riskfaktorer utvärderades som potentiella kriterier för remiss till ett hjärtsviktscenter: systoliskt blodtryck ≤90 mmHg, kreatinin ≥160 µmol/l, hemoglobin ≤120g/l, avsaknad av behandling med RAS-blockad och avsaknad av behandling med betablockad. Förekomsten av 1, 2, eller 3-5 risk faktorer hos patienter yngre än 80 år gav en ett-års överlevnad på 79, 60 respektive 39%.

Riskprediktion i HFpEF
Hjärtsviktsbevakningsdata från fyra områden i USA användes för att studera 2 304 sjukhusinläggningar av patienter med HFpEF. Mortaliteten efter 28 dagar och ett år var 11 respektive 34%. De viktigaste prediktorerna för död var hög ålder, hypoxi, sänkt njurfunktion och lågt hemoglobin.

Slutsatser
Patienter med hjärtsvikt har hög risk för död. Avseende HFpEF är det angeläget med snar utveckling av effektiv behandling. I HFrEF bör däremot befintlig evidensbaserad behandling ökas, och specifikt bör underanvändningen av CRT och ICD uppmärksammas. Levosimendan var under studieperioden det vanligaste inotropa läkemedlet i Sverige. Emellertid behöver effekten av levosimendan som planerad upprepad behandling av kronisk HF studeras bättre. Att använda få och enkla riskfaktorer som kriterier för remittering till ett hjärtsviktscenter kan öka andelen patienter som får optimal tillgänglig behandling. Riskprediktorer för HFpEF kan användas för att identifiera högriskpatienter, vilket bidrar till ytterligare karakterisering av HFpEF-populationen.

LIST OF ORIGINAL PAPERS

Thorvaldsen T, Benson L, Dahlström U, Edner M, Lund L. H.
Use of evidence-based therapy and survival in heart failure in Sweden 2003-2012.
Eur J Heart Fail. 2016 May; 18(5):503-11

Thorvaldsen T, Benson L, Hagerman I, Dahlström U, Edner M, Lund L.H.
Planned repetitive use of levosimendan for heart failure in cardiology and internal medicine in Sweden.
Int J Cardiol. 2014 Jul 15;175(1):55-61

Thorvaldsen T, Benson L, Ståhlberg M, Dahlström U, Edner M, Lund L.H.
Triage of patients with moderate to severe heart failure Who should be referred to a heart failure center?
J Am Coll Cardiol. 2014 Feb 25;63(7):661-71

Thorvaldsen T, Shah A, Cheng S, Agarwal S, Claggett B, Wruck L, Chang P, Rosamond, W, Lewis E, Desai A, Lund L.H, Solomon S.D.
Predicting risk in patients hospitalized for acute decompensated heart failure and preserved ejection fraction: The Atherosclerosis Risk in Communities study Heart Failure Community Surveillance.
In manuscript

LIST OF ABBREVIATIONS

ACEi	Angiotensin-converting enzyme inhibitor
ADH	Antidiuretic hormone
ADHF	Acute decompensated heart failure
ARB	Angiotensin receptor blocker
ARIC	The Atherosclerosis Risk in Communities study
ARNI	Angiotensin receptor neprilysin inhibitor
AUC	Area under the curve
BMI	Body mass index
BP	Blood pressure
BTC	Bridge to candidacy
BTD	Bridge to decision
BTR	Bridge to recovery
BTT	Bridge to transplantation
BUN	Blood urea nitrogen
CRF	Case report form
CRT	Cardiac resynchronization therapy
DT	Destination therapy
ECG	Electrocardiogram
EF	Ejection fraction
ESC	European Society of Cardiology
ESHF	End stage heart failure
GEE	Generalized estimation equations
HF	Heart failure
HFmrEF	Heart failure with mid-range ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HFSS	Heart failure survival score
HTx	Heart transplantation
ICD	Implantable cardioverter defibrillator
ICD codes	International Classification of Disease codes
ICD-9-CM	International Classification of Disease, Ninth revision, Clinical Modification
LBBB	Left bundle branch block
LVAD	Left ventricular assist device
MCS	Mechanical circulatory support
MRA	Mineralocorticoid receptor antagonist
NYHA	New York Heart Association
RAAS	Renin angiotensin aldosterone system
RAS	Renin angiotensin system
SHFM	Seattle heart failure model
SwedeHF	Swedish Heart Failure Registry (RiksSvikt)

INTRODUCTION

Perspective

In the 1990s the term *evidence-based medicine* was launched by a group at McMaster University, Ontario, Canada[1]. It was based on a growing recognition of several factors including that 1) randomization is the best way to avoid bias and confounding, 2) there are variations in treatment practice due to local traditions rather than results from clinical trials and, 3) with the fast growing medical literature there is a need to rank evidence according to quality (good to poor) to guide clinicians in choices of treatment. In the British Medical Journal evidence based medicine was ranked as the 8th most important medical discovery in history of any kind, including antibiotics, vaccines, and the discovery of DNA[1].

During the last decades there have been dramatic advancements in evidence-based interventions for cardiovascular disease. Between 1970 and 2000, life expectancy increased by six years, of which more than four were attributed to reduction in cardiovascular mortality (Figure 1)[2]. These gains were mainly in patients with coronary heart disease, but it is unknown to what extent they reflect improved care of myocardial infarction as opposed to its complications, such as heart failure (HF). Despite advancements in treatment, HF remains associated with poor quality of life and is now a leading cause of death and the leading cause of hospitalization[3].

In this thesis, aspects of evidence-based medicine in HF are studied. To what extent do patient receive evidence-based treatments? What are the current traditions for a treatment with poor evidence? And finally, where gaps in evidence exist, further description of the disease is provided to potentially help targeting future evidence-based treatment.

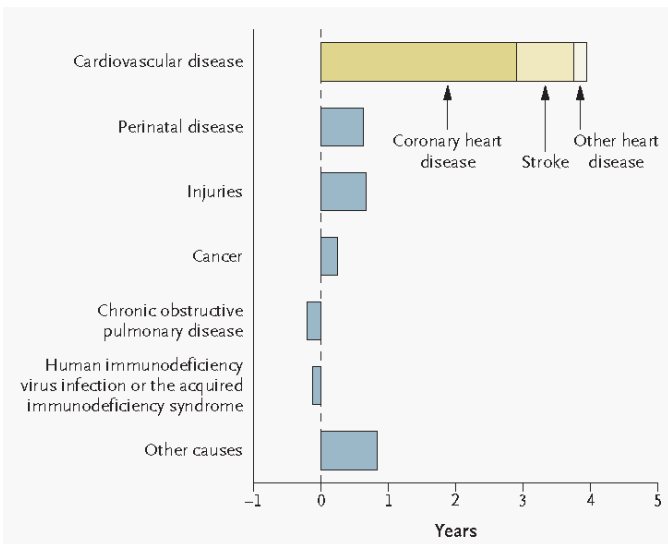

Figure 1. Contribution of different conditions to change in life expectancy between 1970 and 2000 in the USA.
Reproduced with permission from [*Lenfant N Engl J Med.* 2003;349(9)], Copyright Massachusetts Medical Society.

General aspects of heart failure

As defined by the European Society of Cardiology (ESC) "heart failure is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/ or elevated intracardiac pressures at rest or during stress"[4]. We and other authors emphasize the concept of maintained cardiac output due to neurohormonal compensation, which is adaptive in the short run but maladaptive in the long run, leading to progressive cardiac remodeling and the signs and symptoms classic for HF (Wallentin, L [2010]. Akut kranskärlssjukdom. Liber).

The HF population is broadly characterized by ejection fraction (EF): HF with reduced EF (HFrEF) is typically defined as EF <40% and HF with preserved EF (HFpEF) as EF ≥50%. The two entities differ in underlying etiology and comorbidities and in the response to treatment. EF between 40-49% represent a grey-zone with some features similar to HFrEF and some to HFpEF[5]. In the latest ESC guidelines for HF from 2016 the term HF with mid-range EF (HFmrEF) was introduced for this category[4]. HFpEF has not been uniformly defined over the years, with cut-off values for EF used in trials and observational studies ranging from >40% to >55%. In early studies, symptoms of HF in combination with normal EF was typically used as diagnosis criteria for HFpEF. In more recent trials, objective evidence of altered cardiac structure (e.g. enlarged left atrial volume and/or increased left ventricular mass) and function (i.e. abnormal mitral valve inflow patterns and/or mitral annular relaxation velocity) are usually required. The latter criteria are in accordance with the diagnosis criteria for HFpEF in the latest ESC guidelines[4]. The term HFpEF is preferred over the earlier used "diastolic HF" since despite a normal EF, abnormal systolic chamber structure and myocardial function have been shown in these patients[6].

Another way of characterizing HF is to differentiate between chronic stable and acute decompensated heart failure (ADHF). ADHF refers to a rapid onset of, or progressive change in, symptoms and signs of HF. Patients with ADHF may present with volume overload with or without hypoperfusion or with signs of hypoperfusion with or without congestion[7]. About 4% of ADHF admissions present with overt cardiogenic shock[8]. Hospitalization in HF is associated with substantial in-hospital and early post-discharge cardiovascular events[9].

Severity of symptoms is often described by the New York Heart Association (NYHA) classification (Table 1). Severity of symptoms are related to prognosis[10] and in study I-III in this thesis, NYHA class is used as a patient selection criterion.

Table 1. New York Heart Association classification

NYHA	Symptoms
Class I	No limitation of physical activity
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in breathlessness and fatigue
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in breathlessness and fatigue
Class IV	Symptoms at rest may be present. Unable to carry out any physical activity without discomfort.

Epidemiology of heart failure

HF has become a global pandemic with more than 26 million adults suffering from the disease worldwide[11]. The prevalence of HF in the western world is 2-3%[12], and is suspected to rise as the population grows older to reach a projected 25% increase by 2030[13]. HF is the leading cause of hospitalization in patients >65 years of age[14]. The costs for HF amount to 1-2% of all health expenditures in Europe[4] and 75% of the costs are related to in-patient care. HF is associated with poor quality of life and 5-75% one-year mortality, depending on severity[15,16]. Advanced chronic HF refractory to guideline-based medical HF management affects up to 5% of the HF population[17]. Around half of the patients with HF have normal or near-normal ejection fraction[18], mortality in this group is similar or slightly lower compared to in HFrEF[19].

Etiology, risk factors and clinical characteristics

Ischemic heart disease and hypertension are typically seen as the most common causes of HF[4]. Other causes include valvular heart disease, arrhythmias, and cardiomyopathy due to e.g. myocarditis, drug and alchohol abuse[20]. There are several risk factors for the development of HF. In the Framingham Heart Study the following variables were associated with an increased risk of incident HF (either HFpEF, HFrEF or both): Older age, diabetes mellitus, a history of valvular disease, higher body mass index (BMI), smoking, atrial fibrillation, male sex, higher total cholesterol, higher heart rate, hypertension, cardiovascular disease, left ventricular hypertrophy, and left bundle-branch block (LBBB)[21]. Both HFrEF and HFpEF have high comorbidity burdens, but the HFpEF population tend to have more hypertension, atrial fibrillation and chronic kidney disease and less ischemic heart disease[22]. The patients with HFpEF are also more likely to be older and female, and less likely to be African American compared to patients with HFrEF[23]. Furthermore, levels of natriuretic peptides are lower in HFpEF than in HFrEF[24].

Prognosticators in heart failure

Numerous predictors of outcome and risk prediction models have been identified and developed in HF[25]. In a systematic review on risk prediction in HF the following factors were found to be the most commonly used and strongest predictors of mortality in different risk prediction models: Age, renal function, sodium levels, EF, sex, natriuretic peptides, NYHA class, diabetes mellitus, BMI and exercise tolerance (measured as peak oxygen consumption)[26]. Prediction of survival in the individual HF patient is complex. Risk prediction models may be useful in providing patients and family realistic expectations regarding prognosis, but can also be used for patient selection/referral for different therapies. However, many risk prediction models are not suitable for daily clinical practice because they are too complex, time consuming and often require variables not at hand. The Seattle Heart Failure Model (SHFM) and the Heart Failure Survival Score (HFSS) are well validated comprehensive risk models used by HF specialists in the evaluation of candidacy for heart transplantation (HTx) and mechanical circulatory support (MCS)[27,28]. For the general practitioner however, there are no clear guidelines on when to refer patients for evaluation of advanced HF therapy. Therefore, one of the objectives of this thesis was to identify simple clinical parameters that can be used as criteria for referral to HF centers.

Another aspect of risk prediction models is the potential lack of generalizability. Models developed from randomized trials may not be applicable to the general population and

predictors of mortality in HFrEF may not be the same as in HFpEF. Prognosticators in HFpEF are less studied than in HFrEF. In **Study IV** in this thesis, we developed a risk prediction model for a strict HFpEF population admitted to hospital.

Pathophysiology of heart failure

HFrEF

Myocardial stress or injury in HFrEF is followed by a compensatory neurohormonal (mal) adaptation to restore/improve hemodynamics. The three main and most studied neurohormonal pathways are activation of the 1) sympathetic nervous system 2) renin angiotensin aldosterone system (RAAS) and 3) antidiuretic hormone (ADH). In the short term these compensatory mechanisms contribute to maintenance of systemic blood pressure (BP) and restoration of cardiac output through elevations in cardiac contractility, heart rate, vascular resistance and renal sodium and fluid retention. However, in the long term a vicious circle of increased afterload, fluid retention and tachycardia results in disease progression, further myocardial injury and deterioration of cardiac function. The cardiac structural changes occurring in response to the neurohormonal activation is referred to as ventricular remodeling. In HFrEF, typical ventricular remodeling is characterized by left ventricular dilatation, increased end-diastolic volumes and eccentric hypertrophy. A simplified overview of the RAAS is shown in Figure 2.

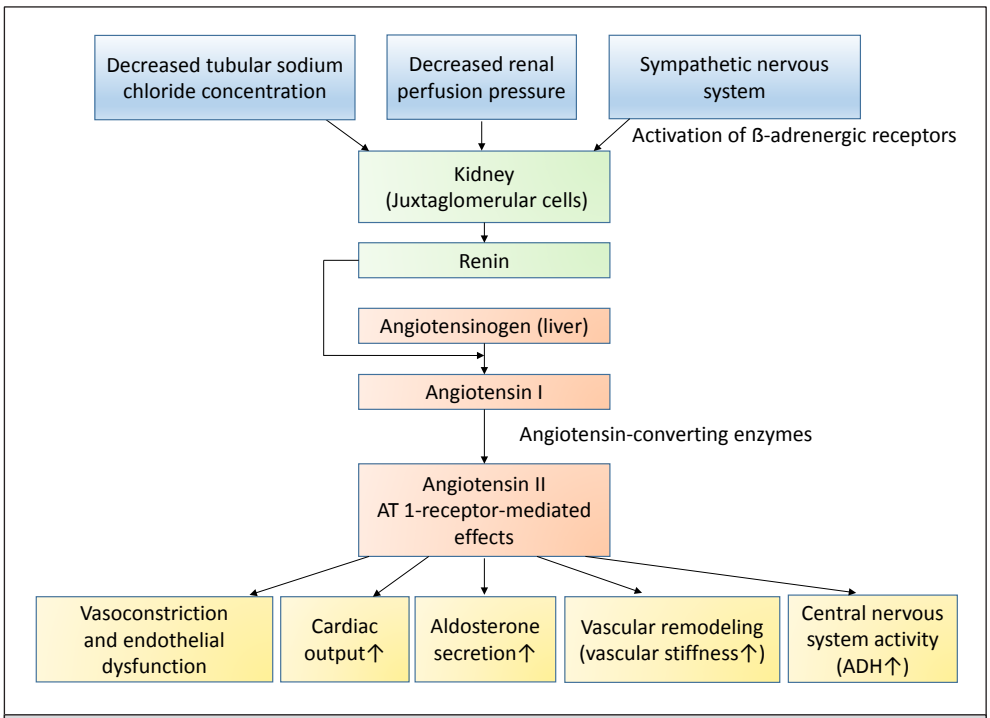

Figure 2. The renin-angiotensin-aldosterone system.
Adapted from *Tomaschitz et al. Nat. Rev. Endocrinol. 2010.6;83-93.*

HFpEF

The pathophysiological pathways of HFpEF are incompletely defined and not as well characterized as in HFrEF. Traditionally, the signs and symptoms of HFpEF have been attributed to hypertensive left ventricular remodeling including increased left ventricular mass, concentric hypertrophy and diastolic dysfunction which in turn leads to development of fibrosis and ventricular stiffness[29]. However, increasing evidence suggest an important role of systemic microvascular endothelial inflammation related to comorbidities in HFpEF as a cause of fibrosis, increased oxidative stress and alterations in cardiomyocyte signaling pathways. These changes may lead to cardiac dysfunction (predominantly diastolic) and microvascular dysfunction[29-31]. Hence, whereas HFrEF is typically triggered by a direct cardiomyocyte damage such as myocardial infarction, HFpEF may be more commonly a result of comorbidity driven endothelial dysfunction affecting the cardiomyocyte over time (Figure 3)[30,31]. Neurohormonal activation exists in both HF entities, but it is thought to play a less dominant role in HFpEF.

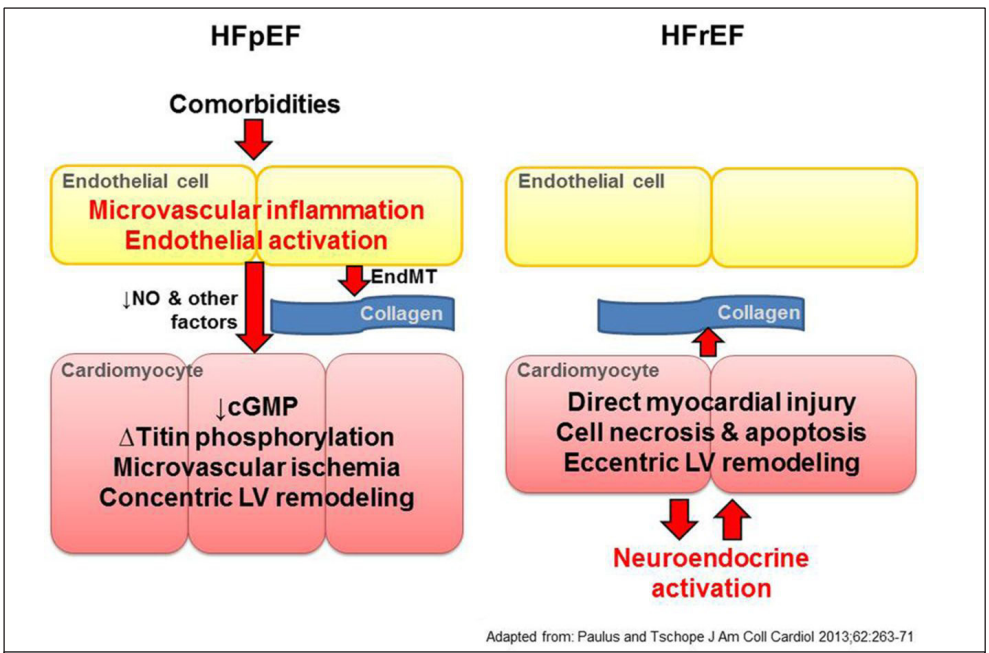

Figure 3. Postulated differences in pathophysiology in HFpEF and HFrEF.
In HFpEF, comorbidities induce a systemic inflammatory state which in turn increases oxidative stress in the microvascular endothelium. Myocardial nitric oxid (NO) availability decreases affecting signaling pathways in adjacent cardiomyocytes; cyclic guanosine monophasphate (cGMP) availability and titin phosphorylation are altered leading to concentric remodeling. Transformation of endothelial cells into fibroblasts (EndMT: Endothelial mesenchymal transistion) produces fibrosis. In contrast, in HFrEF a direct injury on the cardiomyocyte causes cell necrosis, apoptosis and eccentric LV remodeling.
Reproduced from [Heart, Lam CSP, Lund LH, 102, 257-259, 2016] with permission from BMJ Publishing Group Ltd. Original figure from [J Am Coll Card, Paulus, Tschöpe, 62, 263-271, 2013] with permission from Elsevier.

Treatment of HFrEF

Pharmacological treatment

Historically HF was considered a hemodynamic disorder and treatment focused on improving hemodynamic parameters[32]. During the 1980 the understanding of the detrimental role of neurohormonal activation in the progression of HF evolved as "the neurohormonal hypothesis", and blocking the sympathetic nervous system and the RAAS became the foundation of modern HF treatment. The CONSENSUS and SOLVD trials published in 1987 and 1991 showed that the angiotensin converting enzyme inhibitor (ACEi) Enalapril vs. placebo reduced mortality by 27% and 16% in NYHA class IV and II-III respectively[33,34]. Trials of beta-blockers compared to placebo followed about a decade later (CIBIS II, MERIT-HF, COPERNICUS) and showed a mortality reduction of 34-35% in HFrEF[35-37]. For patient intolerant to ACEi, angiotensin receptor blockers (ARB) improve outcomes. This was shown in 2003 in the CHARM-Alternative trial, a randomized controlled trial on candesartan in HFrEF[38]. The treatment with the mineralocorticoid receptor antagonist (MRA) Spironolactone, an agent blocking the RAAS by aldosterone antagonism, resulted in an incremental mortality reduction of 30% when added to ACEi in patients in NYHA class III-IV (the RALES trial)[39]. Subsequently, the EMPHASIS-HF trial from 2011 documented that MRAs were effective also in NYHA class II[40]. In 2014 a new agent was introduced as HF treatment; the angiotensin receptor neprilysin inhibitor (ARNI). By inhibiting neprilysin the degradation of several endogenous vasoactive peptides including natriuretic peptides, bradykinin and adrenomedullin is reduced. ARNI was superior to ACEi in reducing mortality in the PARADIGM trial[41], and in the ESC HF guidelines of 2016 ARNI are recommended as a replacement for ACEi in symptomatic patients[4]. Notably, neprilysin inhibition enhances endogenous compensatory responses, the first time a strategy of enhancing rather than inhibiting compensatory responses has been successful.

In search for new HF treatments other approaches to interrupt the RAAS have been studied, but with negative or neutral findings. Direct renin inhibition instead of ACEi or added to an ACEi did not improve survival [42,43]. Studies on the vasopressin receptor antagonists tolvaptan were also negative in terms of survival benefit[44].

Device therapy

An intraventricular conduction delay (apparent as prolonged QRS-duration on the electrocardiogram, ECG), occurs in 15-30% of patients with HFrEF and often leads to a discoordinated ventricular contraction pattern resulting in reduced systolic function and increased diastolic volume[45]. Cardiac resynchronization therapy (CRT) involves pacing the left and right ventricle simultaneously, or near simultaneously. By overcoming the electric dyssynchrony, CRT induce reverse remodeling with decreased left ventricular volumes. Furthermore, CRT reduces mortality by 22%[46] in NYHA class III-IV and as more recently demonstrated, by 17% in NYHA I-II[47] in selected patients with prolonged QRS duration.

Sudden cardiac death due to ventricular tachyarrhythmia is an important cause of death in HFrEF. The use of Implantable cardioverter defibrillator (ICD) as primary prevention of sudden cardiac death in ischemic and non-ischemic cardiomyopathy reduces mortality by 25-30%[48-50], although this has more recently been questioned in non-ischemic cardiomyopathy[51]. Landmark trials for ICD treatment are MADIT-II showing survival benefit of ICD in post-myocardial infarction patients with impaired left ventricular function[48] and SCD-HeFT that documented survival benefit in ischemic and non-ischemic cardiomyopathies with reduced

EF and NYHA class II-III[50]. The benefit of ICD when combined with CRT is less certain[51,52]. An overview of trials that have contributed to the dramatic advances in the treatment of HFrEF is shown in Figure 4[53].

Advanced therapy: Mechanical assist device and heart transplantation

In severe HF refractory to medical and device therapy, HTx remains the gold standard treatment with a one-year survival of almost 90%[54]. Interestingly, randomized controlled trials have not been performed for HTx, yet the overwhelming consensus is that HTx reduces mortality and improves quality of life in appropriately selected patients[4]. However, due to organ shortage, artificial heart pumps (left ventricular assist devices, LVADs) have been increasingly utilized in these patients. LVADs can be used as 1) a bridge to transplantation (BTT) to maintain end-organ perfusion and survival while waiting for a HTx, 2) as a bridge to decision (BTD) to

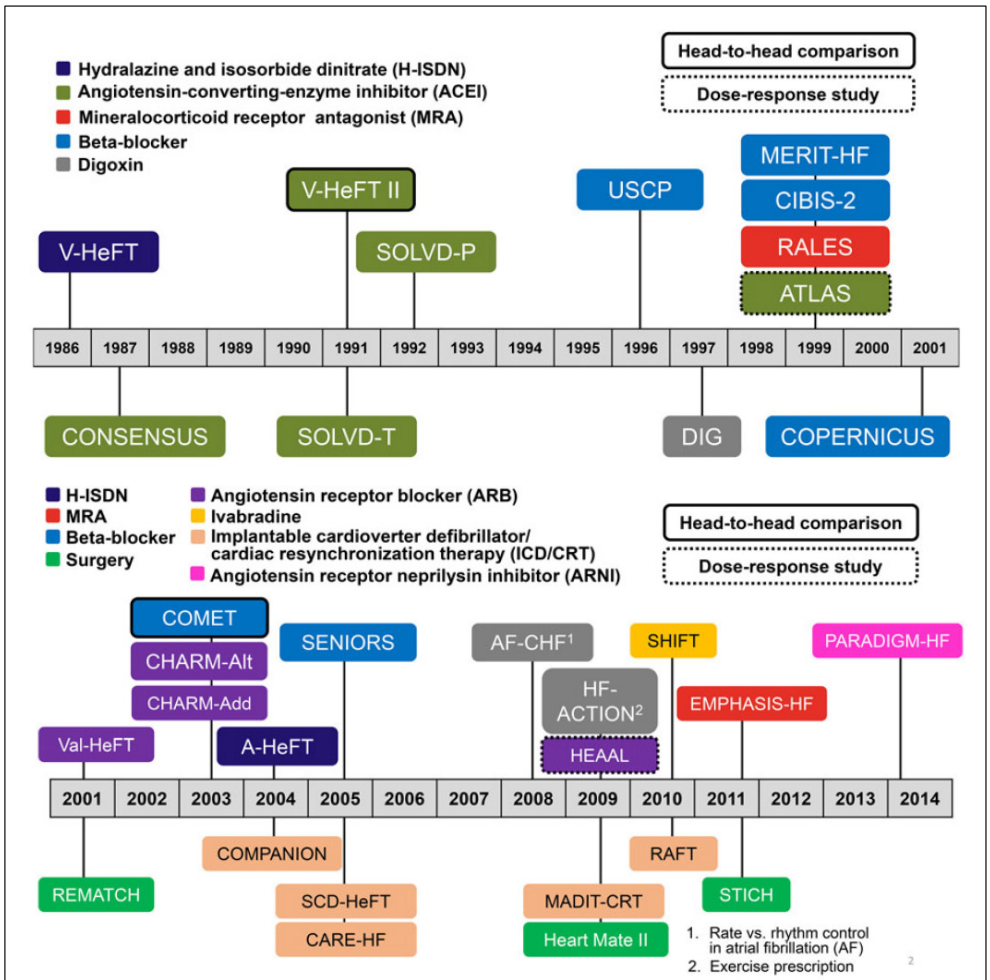

Figure 4. Trials in HFrEF on pharmacological and device treatment 1986-2014.
Reproduced from [McMurray, Improving outcomes in heart failure: a personal perspective. Eur Heart J 2015;36(48):3467-70], by permission of Oxford University Press

allow time for full clinical evaluation for HTx, 3) as a bridge to candidacy (BTC) to improve end-organ function or reverse contraindications in order to become eligible for HTx, and 4) as destination therapy (DT) for patients with contraindications for HTx, and 5) in rare cases for cardiac recovery facilitated by LVAD unloading together with intensive neurohormonal blockade, leading to reverse remodeling, bridge to recovery (BTR)[55].
The landmark trial for LVAD as destination therapy, REMATCH from 2001 showed a relative mortality reduction of 48% for patients in NYHA IV with DT LVAD as compared to medical therapy[56]. One- and two-year survival in the study was 52% and 23% respectively. Today one-year survival with LVAD is >80%[57]. Reasons for this remarkable improvement include better patient selection and improved surgical techniques and post-operative care. More important however, is most likely the advances in LVAD techniques with the introduction of continuous flow type pumps[58]. In 2009 a randomized trial was published comparing the new generation of pumps with continuous flow (HeartMate II) with the earlier generation of pulsatile flow pumps (HeartMate XVE). A significant increase in survival free from stroke and device failure at two years was observed with the continuous flow device[59]. Furthermore, the latest version of continuous flow pumps with fully magnetically levitated centrifugal-flow (HeartMate III) was superior to pumps with axial-flow (HeartMate II) with regard to 6 months outcomes (mainly due to less reoperations for pump malfunctions)[60]. Very recently, in the ENDURANCE trial, the centrifugal-flow LVAD (Heartware) as DT was proved to be non-inferior to the axial-flow LVAD (HeartMate II) with regards to survival free from disabling stroke and device removal[61]. However, despite technological improvements, LVAD therapy remains associated with a high risk of serious complications including stroke, bleeding, pump thrombosis and infections[57].

Advanced therapies with HTx and LVAD therapy are thought to be underutilized[17,62]. In the US, an estimated 100,000 would benefit from HTx[62], yet there are only 2,500 performed annually[54]. The main explanation for this is organ shortage[63]. For LVADs around 25,000–250,000 patients are estimated to benefit in the US, primarily as DT[17], and around 2,500 LVAD implantations[57] are performed annually. The main reason for underutilization of LVAD is unknown. A small pilot study identified numerous LVAD candidates through systematic screening, suggesting that potential candidates are not recognized in routine clinical care[64].

Treatment of HFpEF

In HFpEF, no treatment has yet been convincingly shown to improve outcomes. Treatment recommendations are based on expert consensus (not clinical trial results) and include relief of volume overload, strategies to improve symptoms and treatment of coexisting conditions. Randomized controlled trials of ACEi, ARBs and MRAs have all failed to show improved survival in HFpEF[65,66]. Randomized controlled trials of beta-blockers in HFpEF are small and data are conflicting[67,68].

Theories on why trials are negative or neutral include insufficient power, inadequate diagnostic criteria for HFpEF and patient heterogeneity. The difficulty of diagnosing HFpEF was illustrated in a post-hoc analysis from the TOPCAT trial on spironolactone in HFpEF. Regional differences between the Americas and Russia/Georgia was observed both in characteristics, event rates and effect of spironolactone and the authors argue that the patients from Russia/Georgia were healthier and maybe not “true” HFpEF patients[69].

A randomized trial on ARNI in HFpEF (PARAGON, Clinical Trials.gov number NCT01920711) is ongoing. Inclusion criteria are predefined structural changes on Echo, elevated natriuretic peptides, HF symptoms and EF ≥45%.

HFpEF is a complex syndrome with a substantial patient and phenotype heterogeneity. One theory is that a "one-fits-all" treatment is not effective in HFpEF and that an individualized treatment approach based on different patient and etiology phenotypes is necessary[70]. Hence further characterization of HFpEF with regard to pathophysiology and predictors of prognosis may be an important step in identifying key areas of potential intervention. In **Study IV** in this thesis we identify predictors of mortality in a HFpEF population hospitalized with ADHF.

Treatment of ADHF

No treatment has yet been shown to have effect on outcomes in ADHF[71]. Treatment recommendations for ADHF focus on relief of symptoms and treatment of underlying disease. In the ESC guidelines for acute HF, diuretics, vasodilators, inotropic agents and vasopressors are recommended for symptom relief, all with a class I or II recommendation and level of evidence B or C. Inotropic agents are *not* recommended unless there are signs of hypoperfusion or the patients is symptomatically hypotensive (class III recommendation)[4].

Inotropic agents

Intravenous inotropic agents are used to treat acute and in some cases chronic HF with concomitant low output, in order to maintain systemic perfusion and preserve end-organ function. Conventional inotropes traditionally used are milrinone, dobutamine and dopamine. Milrinone is a phosphodiesterase inhibitor that increases myocardial calcium concentrations and contractility, induces vasodilation and decreases afterload and filling pressures by preventing degradation of cyclic adenosine monophosphate (cAMP).

Dobutamine is a catecholamine that acts mainly on $beta_1$-adrenergic receptors, but also imposes minimal effect on $beta_2$- and $alpha_1$- receptors. Hemodynamic effects include increased stroke volume and cardiac output with a modest decrease in systemic vascular resistance[72].

Dopamine is an endogenous catecholamine that in low dose acts on $dopamine_1$-receptors dilating various vascular beds including renal and coronary. At intermediate doses dopamine stimulates $beta_1$-adrenergic receptors and increases cardiac output by increasing stroke volume. At high doses, dopamine acts as an alpha-receptor agonist causing vasoconstriction and increased afterload.

The use of these intravenous inotropic agents is deemphasized by American and European guidelines because of lack of adequately powered randomized trials and the adverse-event risk profile. The adverse impact on outcomes reported include induced myocardial ischemia, arrhythmias and increased mortality[73-75].

Levosimendan is a relatively novel inotropic agent that was approved in Europe in the 2000s for the treatment of advanced acute HF. It is not licensed in the USA. Levosimendan is a myofilament calcium sensitizer that stabilizes the interaction between calcium and troponin C by binding to troponin C in a calcium dependent manner. Thereby, inotropy is increased with no or minimal increase in oxygen demand[76]. Levosimendan also acts as an adenosine triphosphate-dependent potassium channel opener in the sarcolemma of vascular smooth

muscle cells and in the mitochondria in cardiomyocytes[77]. Observed effects of levosimendan are increased myocardial contractility, reduction in filling pressures and dilation of arterial, venous and coronary vessels[78].

The half-life of levosimendan is about one hour and enables fast onset drug action. However, the active metabolite of levosimendan, OR-1856, is formed slowly and has a half-life of about 75 to 80 hours, allowing cardiovascular effects to persist up to 7-9 days after treatment[79].

The early trials LIDO and RUSSLAND suggested that levosimendan improves hemodynamics and survival compared to dobutamine and placebo, respectively[80,81], but the survival benefit was not confirmed in the larger SURVIVE and REVIVE trials[82,83]. A meta-analysis from 2012 suggests an association between use of levosimendan and a reduction in mortality, but larger randomized trials sufficiently powered for mortality outcome are currently lacking and called for[84].

In clinical practice levosimendan is often used as planned repetitive infusions in severe chronic HF. In an expert panel document from 2014 based on 9 studies out of which 6 were randomized, the authors concluded that there is evidence of improvements in hemodynamics, symptoms, rehospitalization rates and biomarkers with the use of repetitive levosimendan in stable HF, regarding survival benefit further studies are needed[85].

Hence, the beneficial effects of levosimendan in acute HF and as planned repetitive treatment are uncertain. In **Study II** in this thesis we aimed to describe the extent of levosimendan treatment for these two indications in Sweden.

AIMS

The overall aim of this thesis is to describe contemporary patients with HF, with both reduced and preserved EF with regards to mortality and markers of poor prognosis, and for HFrEF to study patterns of modern treatments and indications for referral to a HF center.

Specific aims are

1 To investigate in HFrEF:
- How is implementation of evidence-based treatment over time?
- What is survival over time?
- Is implementation of evidence-based treatment associated with changes in survival? **(Study I)**

2 To assess the use of levosimendan vs. conventional inotropes and the use of levosimendan as planned repetitive vs. acute treatment for HF in cardiology and internal medicine in Sweden. **(Study II)**

3 To describe the Swedish country-wide contemporary prognosis in NYHA class III-IV HFrEF and to identify simple independent predictors of prognosis that can be used as criteria for referral to a HF center. **(Study III)**

4 To identify predictors of 28-day and one-year mortality in patients hospitalized with ADHF and preserved EF and to use these predictors to create risk scores for short and intermediate-term mortality at hospital admission. **(Study IV)**

PATIENTS AND METHODS

A summary of the data used in this thesis is shown in Table 2.

Data source

Studies I-III

For **Studies I-III**, data from the Swedish Heart failure registry (SwedeHF) is used. The Swedish heart failure registry (www.swedehf.se) is a nationwide continuous health quality and research registry founded in 2000 by Ulf Dahlström, Linköping, Sweden and Magnus Edner, Stockholm, Sweden. By 2016 the registry contained more than 70,000 patients from

Table 2. Overview of the data used in this thesis.

Study	I	II	III	IV
Data source	SwedeHF	SwedeHF	SwedeHF	ARIC Heart Failure Community Surveillance
Time of data collection	2003-2012	2000-2011	2000-2013	2005-2012
Study population	NYHA class II–IV, EF <30% and duration of heart failure ≥6months	a) Patients with confirmed use of inotropes b) In-patient controls: NYHA III-IV, EF <40%	NYHA class III-IV EF <40%	Hospitalizations with acute decompensated heart failure and EF ≥50%
Design	Registry based	Registry based	Registry based	Registry based
Numbers in study population	5,908	Inotrope use: 655 in-patient controls: 6,069	10,062	2,304 (weighted sample 10,789)
Outcomes	1) Implementation of evidence-based treatment over time 2) Survival over time	1) Levosimendan use in ADHF 2) Extent of planned repetitive use of levosimendan	One-year mortality by number of pre-specified risk factors	28-day mortality and one-year mortality from hospital admission
Adjustments	38+5 variables	None	46 variables	33 variables
Main statistical analyses	Modified Poisson regression with adjustment using generalized estimation equations	Descriptive comparison between groups including Kaplan Meier survival analysis	Relative survival modeling with Kaplan-Meier analysis Cox proportional hazards regression	Stepwise logistic regression

SwedeHF, Swedish Heart Failure Registry; ARIC, Atherosclerosis in the Community; NYHA, New York Heart Association; EF, ejection fraction; ADHF, acute decompensated heart failure.

about 75% of the hospitals in Sweden and about 10% of primary care clinics. Inclusion criteria is clinical-judged heart failure and both hospitalizations and out-patient visits are reported to the registry. EF is not required, but recorded in around 90%. Patients may be registered several times and at an early or late stage in the timeline of their disease. First registration does not necessarily mean new-onset HF. Around 80 variables are recorded and entered on-line into a database managed by the Uppsala Clinical Research Center. The database is run against the Swedish death registry monthly. Informed consent is not necessary, but patients are allowed to opt out. The establishment of the registry and all studies receive ethics approval. The case report forms are available at www.swedehf.se.

Coverage has varied somewhat over the years and calculations are complex. In the latest annual report from 2015 coverage was 54%, calculated as all unique patients in the registry from 2014 with an echo performed, divided by all hospitalized patients in Sweden with a primary discharge diagnosis of HF in 2014. Coverage is based on active centers defined as hospitals with more than 10 registrations in SwedeHF that year. In primary care coverage is much lower.

SwedeHF is financed by the federal government through the Swedish Association of Local Authorities and Regions.

Study IV

Study IV is based on data from the Heart Failure Community Surveillance in the Atherosclerosis Risk in Communities Study (ARIC). ARIC is a prospective epidemiologic study conducted in four U.S. communities (Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota; and Washington County, Maryland). The HF Community Surveillance component of ARIC conducts surveillance of inpatient HF in patients aged ≥55 years beginning in 2005 and ongoing. The objectives of the HF Surveillance are to monitor long term trends in HF hospitalizations and to provide a platform for ancillary studies.

Eligible hospitalizations are those with a HF related discharge diagnosis in any position (International Classification of Disease, Ninth revision, Clinical Modification [ICD-9-CM], table 3). The number of cases meeting the eligibility criteria is reduced by applying various sampling fractions to different classes of ICD9-CM codes (428 and non-428). The sampling fractions or probabilities are defined by age, sex, race and community of residence. This procedure is established in order to achieve a balance in the number of events between field center, sex, and race groups so that precision of event rates estimates will be similar across these strata.

Abstraction from the medical record is performed by trained personnel. Detailed abstraction is performed if there is evidence of symptoms related to HF or physician documentation of HF as the reason for hospitalization, otherwise the hospitalization is classified as unlikely and no further abstraction is performed. All hospitalizations are classified by a computer based algorithm or physician review, and given an ARIC classification of HF defined as 1) definite ADHF, 2) possible ADHF, 3) chronic stable HF, 4) HF unlikely, and 5) HF unclassifiable. If there is evidence of increased worsened HF symptoms and intensified HF therapy ADHF is selected.

The ARIC Study is carried out as a collaborative study supported by National Heart, Lung and Blood Institute.

Table 3. Description of eligible international classification of disease (ICD) codes used to sample potential Heart Failure hospitalizations in the ARIC HF Surveillance.

ICD-9_CM	Disease classification
398.91	Rheumatic heart disease
402.01	Hypertensive heart disease-malignant with congestive heart failure
402.11	Hypertensive heart disease-benign with congestive heart failure
402.91	Unspecified hypertensive heart disease with congestive heart failure
404.01	Hypertensive heart disease and renal failure- malignant with congestive heart failure
404.03	Hypertensive heart disease and renal failure- malignant with congestive heart and renal failure
404.11	Hypertensive heart disease and renal failure- benign with congestive heart failure
404.13	Hypertensive heart disease and renal failure- benign with congestive heart and renal failure
404.91	Hypertensive heart disease and renal failure- unspecified with congestive heart failure
404.93	Hypertensive heart disease and renal failure- unspecified with congestive heart and renal failure
415.0	Acute cor pulmonale
416.9	Chronic pulmonary heart disease, unspecified
425.4	Other primary cardiomyopathies
428.x	Congestive heart failure
518.4	Acure edema of lung, unspecified
786.0x	Dyspnea and respiratory abnormalities

Study I

Aim

To investigate in HFrEF:

- How is implementation of evidence-based treatment over time?
- What is survival over time?
- Is implementation of evidence-based treatment associated with changes in survival?

Patients

5,908 unique patients with EF<30%, NYHA class II-IV in SwedeHF between January 2003 and May 2012 were included in the main analysis.

Protocol

The evidence-based treatment studied were: renin angiotensin system (RAS) antagonists (ACEi and or ARB), beta-blockers, MRA, CRT and ICD.

We assessed patient characteristics and crude and risk-adjusted evidence-based treatments and survival over time. We adjusted for 38 variables plus the five evidence-based therapies. Analysis was performed in a cross-sectional manner, individuals were not followed over time.

We performed separate sensitivity analyses as follows:

1) Drug dosing defined as percent of target dose for the studied treatments
2) Analysis of the main study population, but with risk-adjustment restricted to those variables that changed significantly over time (21 variables)
3) A separate analysis for those centers that participated during the whole study period (11 centers)
4) For patients with more than one registration, assessment of changes in therapies between first and last visits
5) Separate analyses for patients seen in cardiology and internal medicine/geriatrics
6) A separate analysis of CRT and ICD use including only centers performing device implantation
7) An opportunity-based score measured as the number of treatments divided by the number of indicated treatments and an all-or-none score measured as the number of patients with all indicated treatments divided by the number of patients eligible for all interventions
8) A separate analysis for patients with EF <40% including NYHA I-IV and any duration of HF

Endpoints

Endpoints were

1) The use of evidence-based treatment over time.
2) Survival over time:
    a. One-year and three-year survival post discharge or out-patient visit for the whole study population
    b. 30-day survival post discharge for the hospitalized patients

Study II

Aim

To describe the use of levosimendan vs. conventional inotropes and the use of levosimendan as planned repetitive vs. acute treatment for HF in cardiology and internal medicine in Sweden.

Patients

Patients in SwedeHF between 2000 and 2011 with confirmed inotrope use through validation were studied and compared to controls of in-patient registrations with NYHA III-IV and EF <40%.

Protocol

Validation of inotropic treatment: In the early version of the registration case report form (CRF) in SwedeHF the variable “received inotropes” was a yes/no variable and indication was not recorded. We performed a validation as follows: For centers with ≥ 1 registration with “received inotropes” =yes, the local SwedeHF-administrator was asked to control the medical history of the patients and complete a CRF on inotropic treatment (Figure 5).

SwedeHF Validation of treatment with an inotropic agent

1. **Personal identification number: _____**

2. **Date of registration: _____**

3. **Type of registration:**

□ Hospitalization
□ Out-patient visit
□ Visit is not documented in the medical records

4. **Administration of an inotropic agent:**

□ Yes, at the registered visit
□ Yes, but at different visit. Date of administration of the inotropic agent: ____
□ No, no administration of an inotropic agent at the registered visit nor at prior visits, go to item 7

5. **Type of inotropic agent: (more than one alternative possible)**

□ Levosimendan (Simdax)
□ Dobutamine (Dobutrex)
□ Milrinone (Corotrop)
□ Dopamine (Giludop, Abbodop, Intropin)
□ Other inotropic agent _____

6. **Indication for treatment with inotropes. If not clearly stated, check the most probable indication. If more than one indication is given, check the main indication:**

□ Peri-operative*, heart surgery
□ Peri-operative*, other surgery
□ ACS-STEMI
□ ACS-NSTEMI
□ Pulmonary edema
□ Renal failure
□ Chock/hypoperfusion
□ NYHA IV
□ Increased body weight
□ Deterioration of heart failure
□ Planned treatment**
□ Other _____

* Peri-operative is defined as administration by an anesthesiologist/in the intensive care unit.
**If the patient was admitted for planned treatment, always check this box, even if other alternatives are true also.
ACS: acute coronary syndrome, STEMI: ST-elevation myocardial infarction
NSTEMI: non-ST-elevation myocardial infarction

7. **If the answer in item 4 is no, check whether the patient received any of the following:**

□ Cordarone (By mistake taken for an inotropic agent?)
□ Digoxine (digoxin has inotropic properties, but is generally not considered inotropic medication)
□ No documentation of any inotropic agent can be found. Likely a mistake in registration

Figure 5. case report form for validation of levosimendan in SwedeHF.

For analysis, the indications for inotropic treatment from the CRF were combined to: acute coronary syndrome (STEMI and NSTEMI), acute peri-operative (heart and non-heart surgery), ADHF (increased body weight, NYHA IV, deterioration HF, chock/hypoperfusion, renal failure), unknown, and planned repetitive.

For general comparison of levosimendan treated patients, we selected a control group from the registry. Attempting to find patients with similar features as those with inotrope treatment, we defined controls as in-patient registrations with NYHA class III-IV and EF <40%.

Individual patients (first registration if more than one) were used for patient characteristics and survival analysis. Registrations and not necessarily unique patients were used to assess overall levosimendan use and planned repetitive levosimendan use as a proportion of all registrations at each center.

We assessed descriptive Kaplan-Meier survival curves for planned repetitive levosimendan, acute levosimendan and controls. Because standard criteria for inotrope use such as shock, respiratory failure and oliguria, are not captured in the registry, adequate statistical adjustment was not feasible and assessment of association between treatment and survival was not performed. For patients receiving planned repetitive levosimendan infusions, we assessed potential indications for device treatment, HTx and LVAD therapy. Potential indications were defined as follows: the respective treatment not already present, and EF<40% and QRS≥120 ms for CRT; EF <40% for ICD; EF<40% and age≤65 for HTx, EF <30% and age ≤75 for LVAD- DT.

Endpoints
We performed a descriptive study of the use of levosimendan in Sweden. No statistical analysis was undertaken to identify associations between treatment and outcome.

Study III

Aim
To describe the Swedish country-wide contemporary prognosis in NYHA class III-IV HFrEF and to identify simple independent predictors of prognosis that can be used as criteria for referral to a HF center.

Patients
10,062 unique patients with EF<40% and NYHA class III-IV in SwedeHF between 2000 and 2013 were analyzed.

Protocol
We divided the study population into three age groups; ≤65, 65-80 and >80 years of age.

Five simple and universally available risk factors were defined based on 1) previously shown properties of poor outcome in HF and 2) availability in daily practice. For descriptive purposes the prognostic impact of 12 additional variables were also assessed.

The five predefined risk factors were: systolic BP <90 mmHg, creatinine >160µmol/l, hemoglobin ≤120 g/l, no treatment with RAS-antagonist, no treatment with beta-blocker.

Endpoints
Observed and expected all-cause mortality by 3 age-groups

Prognostic impact of 1) the five predefined risk factors independently and 2) the cumulative number of the same five risk factors

Study IV

Aim

To identify predictors of 28-day and one-year mortality in patients hospitalized with ADHF and preserved EF and to use these predictors to create risk scores for short and intermediate-term mortality at hospital admission.

Patients

A total of 2,304 hospitalizations (weighted sample 10,789, accounting for sampling fractions) of patients classified as ADHF with an EF ≥50% were included. Patients with a prior reduced ejection fraction ("normalized" EF) and EF missing were excluded. Only ADHF at admission was included. Further, race other than black or white was excluded due to a very low number. Hospitalizations with unknown follow up were also excluded.

Protocol

Thirty-three potential predictor variables were selected based on prior knowledge, clinical relevance and availability at the time of presentation.

The derivation sample comprised data from 2005 through 2011. Validation was performed in data from 2012.

Based on the prognostic impact of the selected variables in the derivation sample, risk scores for 28 days and one year were created. The validation sample was used to validate the risk scores.

Endpoints

All-cause mortality at 28 days and at one year from admission date.

Statistics

Statistics in **study I-III** was performed in R version 2.15.3. Statistics in **study IV** was performed using Stata version 14.1.
The level of significance was set to 5% and all reported p-values and confidence intervals are 2-sided.
Unless otherwise stated, continuous variables were expressed as mean (standard deviation) and categorical variables as n (%).

Study I

Trends in characteristics over time were assessed with Mantel–Haenszel $\chi 2$ test and linear regression. Linearity for the continuous variables (including year) was investigated using restricted cubic splines and plotting the functional form.

Crude and risk-adjusted use of therapy and survival over time were assessed with regression models using generalized estimation equations (GEE). The GEE method may be used when individuals within a "cluster" cannot be assumed to be independent with regard to the variable of interest. In our study the outcomes may be related within hospitals (cluster). The GEE method uses weighted combinations of observations to extract the appropriate amount of information from correlated data[86]. When the probability of an outcome is low (<10%) the difference between odds ratios and relative risk is negligible. In our study the utilization of therapy and survival were generally expected to exceed 10%. Since risk ratios provide

estimates of probability directly, they are more intuitively understood and often preferred to odds ratios in epidemiological studies. We therefore estimated rate ratios directly by using Zou's modified Poisson regression and robust variability adjustment with GEE[87]. Thirty-eight covariates plus the five evidence-based treatments were included in the risk-adjustment model. Risk-adjusted rates are obtained by multiplying the risk ratios from the multivariable model by the observed rate from the reference year 2003. Risk-adjusted rates represent estimated use of treatment and survival assuming patient characteristics were identical to those in 2003.

To avoid bias due to variables missing not at random, we performed multiple imputation (using10 imputations).

Study II
Continuous data is shown as median (interquartile range) and n (%). Groups were compared using Mann-Whitney U or Fischer's exact test. Survival was assessed by Kaplan-Meier analysis.

Study III
The impact of HF in comparison with expected survival in a comparator population can be assessed by relative survival analysis[88]. Expected survival is defined as the survival that would have been observed in the absence of HF. The survival in the Swedish general population, matched by age, gender and year of observation was used as expected survival (obtained from the Human Mortality database, http://www.mortality.org). Observed and expected survival were assessed by Kaplan-Meier analysis. The mortality associated with the HF diagnosis can be defined as the "excess mortality" and is measured as the difference between the observed and the expected mortality[88].

The prognostic impact of the five predefined risk factors was assessed in a multivariable Cox proportional hazards regression analysis adjusting for 46 variables. The prognostic impact of additional 12 other variables was assessed for descriptive purposes. The proportional hazards assumption was tested by scaled Schoenfeld residuals.

The prognostic impact of the cumulative number of risk factors was assessed in a new multivariable Cox proportional hazards regression analysis where a new variable was defined as "number of risk factors present" and adjustment was performed with 42 variables.

Multiple imputation was performed to avoid bias due to variables missing not at random.

Mortality was assessed with Kaplan-Meier statistics for each of the five risk factors and for the cumulative number of the five risk factors. The discrimination of the two regression models was assessed by C-index.

Study IV
Patient characteristics were compared between patient dead vs. alive at 28 days and at one year by Rao-Scott $\chi 2$ test and t-test.

Simple imputation using the sample mean for missing values was performed for variables with >5% missing.

The procedure of creating a risk score was performed separately for 28-day and one-year mortality. Potential covariates for a risk prediction model were entered in a stepwise forward logistic regression. A p-value <0.02 was used as criteria for entering the model. Variables

were then removed in a stepwise fashion until discrimination of the model was impacted (defined as a reduction in the area under the curve [AUC] by 0.015 from the full model). Calibration of the models was performed by Hosmer-Lemeshow statistics.

The coefficients from the logistic regression models (log of the odds ratios) were converted into integer points in a risk score and continuous variables were divided into convenient intervals. The summation of risk points yields the probability of dying at 28 days and one year respectively. Discrimination of the risk scores was assessed by AUC values and calibration by Hosmer-Lemeshow statistics and by plotting observed vs. predicted values.

Validation was performed by assessing discrimination and calibration of the risk scores in the validation sample.

Statistical analyses accounted for the stratified sampling design and weighted by the inverse of the sampling probability.

Ethical considerations

Study I-III: Establishment of SwedeHF and data analyses from the registry are approved by a multisite ethics committee.

Study IV: Each ARIC Study field center and the coordination ARIC Study center have obtained Institutional Review Board approvals.

All studies were conducted in accordance with the declaration of Helsinki.

RESULTS

Study I

From January 2003 to May 2012, 67 of approximately 75 hospitals and 99 of approximately 1000 primary care out-patient clinics reported to the registry. Of the 74,484 registrations, there were 5,908 unique patients with EF <30%, NYHA class II-IV and HF duration ≥6 months.

The number of centers reporting to the registry increased over time from 32 in 2003-2005 to 104 centers in 2009-2012. Mean age was 72 years and 23% were women. Over all, patient characteristics remained stable over time. Significant changes over time included an increase in statin use, a decrease in diuretic, nitrate and digoxin use and an increase in the proportion of patients with hypertension and NYHA class II. Referral to HF nurse-based clinic and hospital-based follow up (as opposed to primary care) also increased significantly over time.

Crude utilization of treatment over time is displayed in Figure 6. Risk-adjusted therapies for the main study population and for the sensitivity analysis on 1) patients seen by cardiologists, 2) patients seen in internal medicine/geriatrics and 3) centers performing device implantation (only for the treatments CRT and ICD) are depicted in table 4. In the main study population, the risk-adjusted use of RAS antagonists and beta-blockers was >85% with minimal changes over time. The use of MRAs decreased significantly from 53 to 42%, risk-adjusted. There was a borderline significant increase in the risk-adjusted use of CRT from 2.4 to 8.2% (p for trend 0.074). The use of ICDs increased significantly from 4.0 to 10.7%, risk-adjusted. The use of device therapy was somewhat higher for patients seen by cardiologist and patient treated in hospitals performing device implantation as compared to patients seen in internal medicine/geriatrics and to the overall study population. Less than 50% of the patients had target doses of RAS antagonists and beta-blockers (Table 5).

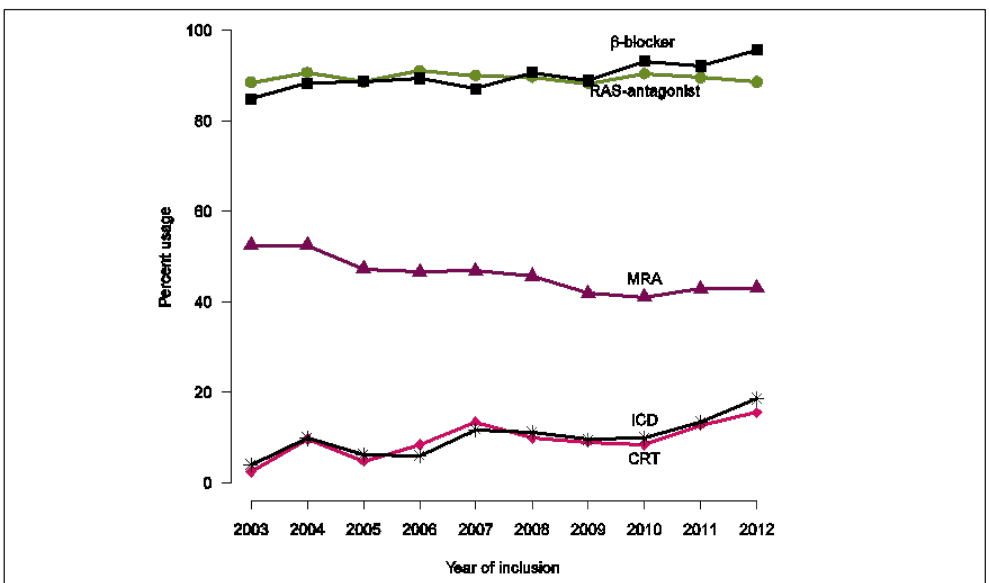

Figure 6. Crude use of evidence-based treatment over time.
RAS, renin angiotensin system; MRA, mineralocorticoid receptor antagonists; CRT, cardiac resynchronization therapy; ICD implantable cardiac defibrillator

Crude and risk-adjusted survival over time are shown in Figure 7 and Table 6 respectively. There were minimal non-significant changes in risk-adjusted survival; 30-days survival increased from 92 to 94%, one-year survival decreased from 81 to 77%, and three-year survival decreased from 58 to 54%. For one- and three-year survival somewhat better numbers were observed for patients seen by cardiologist (no statistical comparison was performed).

Additional sensitivity analyses

Analysis with adjustment restricted to variables with significant change over time and analysis including only the first 11 centers showed similar results as the main analysis apart for a higher MRA use in the 11 centers. When comparing first and last visit, treatment cross-over was seen in both directions with a 54% increase in beta-blockers for the untreated at first visit. MRA treatment was discontinued in 30% and device therapy was added in 11 to 13% of the untreated at first visit.

In both the opportunity-based and the all-or-none scores, a significant increase was seen over time. For details on these sensitivity analyses we refer to supplementary tables in the original article (Supplementary Tables S2-S6 and S12-S13)[89].

Table 4. Risk-adjusted evidence-based treatment over time.
Sensitivity analysis I, Patients seen by cardiologist; Sensitivity analysis II, patients seen in internal medicine/ geriatrics; Sensitivity analysis III, hospitals performing device implantation (only for CRT and ICD)

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	RR per year (95% CI)	P for trend
RAS-antagonists												
Main study population	**88.4**	**91.2**	**90.2**	**91.8**	**89.5**	**89.2**	**87.8**	**89.7**	**87.9**	**86.0**	**0.99 (0.99-1.00)**	**0.091**
Sensitivity analysis I	90.2	91.4	92.0	91.8	90.0	89.5	89.2	90.8	89.6	89.7	1.00 (0.99-1.00)	0.492
Sensitivity analysis II	84.6	92.8	88.1	92.5	90.2	90.8	87.5	89.7	86.2	81.6	0.99 (0.98-1.00)	0.148
Beta-blockers												
Main study population	**84.8**	**88.3**	**89.2**	**89.0**	**86.0**	**89.4**	**87.8**	**91.7**	**90.4**	**93.4**	**1.01 (1.00-1.01)**	**0.008**
Sensitivity analysis I	83.5	91.0	89.4	91.9	87.3	91.3	87.8	92.1	90.1	93.4	1.00 (1.00-1.01)	0.079
Sensitivity analysis II	87.5	84.1	88.3	85.6	83.7	86.8	86.7	91.8	91.1	95.4	1.01 (1.01-1.02)	0.001
MRA												
Main study population	**52.5**	**53.7**	**48.5**	**49.3**	**47.0**	**46.4**	**42.8**	**41.8**	**42.9**	**41.7**	**0.97 (0.95-0.99)**	**<0.001**
Sensitivity analysis I	54.8	61.8	50.2	50.4	46.6	46.5	44.0	41.6	43.5	45.3	0.96 (0.95-0.99)	0.001
Sensitivity analysis II	47.4	44.4	45.2	45.1	44.0	40.8	37.9	39.3	39.9	36.9	0.97 (0.95-1.00)	0.029
CRT												
Main study population	**2.4**	**6.2**	**3.5**	**7.0**	**8.0**	**6.5**	**6.0**	**6.1**	**7.4**	**8.2**	**1.04 (1.00-1.08)**	**0.074**
Sensitivity analysis I	2.4	7.2	3.7	7.8	9.4	7.3	7.4	7.2	8.9	8.6	1.04 (0.99-1.09)	0.100
Sensitivity analysis II	2.5	7.5	6.0	7.3	7.1	7.9	5.1	5.4	6.5	9.4	1.01 (0.94-1.07)	0.861
Sensitivity analysis III	2.7	8.1	4.7	9.8	9.7	8.3	8.4	6.7	9.8	10.0	1.04 (0.98-1.10)	0.249
ICD												
Main study population	**4.0**	**7.0**	**5.8**	**4.7**	**6.8**	**7.9**	**6.8**	**7.2**	**8.4**	**10.7**	**1.07 (1.02-1.11)**	**0.004**
Sensitivity analysis I	4.7	8.7	5.3	4.7	8.5	8.7	8.3	8.1	9.7	13.9	1.08 (1.02-1.14)	0.006
Sensitivity analysis II	2.5	4.9	6.7	4.7	5.0	8.7	5.1	7.1	8.5	6.4	1.06 (0.99-1.13)	0.105
Sensitivity analysis III	5.3	10.1	8.4	6.1	11.5	11.6	12.2	10.6	10.6	12.7	1.05 (0.99-1.10)	0.086

RAS, renin angiotensin system; MRA, mineralocorticoid receptor antagonists; CRT, cardiac resynchronization therapy; ICD implantable cardiac defibrillator

Table 5. Percent of target doses for RAS-antagonists and beta-blockers over time. (crude and risk adjusted).

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	RR per year (95% CI)	P for trend
Crude												
RAS-antagonists (%)												
% of target dose												
≤50	46.8	50.0	48.4	50.7	46.4	44.0	49.4	50.2	50.4	42.2	1.00 (0.98-1.02)	0.946
51-99	6.3	7.8	6.9	8.1	7.7	7.4	7.3	7.6	8.6	12.2	1.03 (0.99-1.08)	0.135
≥ 100	46.8	42.2	44.7	41.1	45.9	48.6	43.3	42.2	41.0	45.6	0.99 (0.97-1.02)	0.645
Beta-blockers (%)												
% of target dose												
≤50	64.1	70.9	66.1	66.5	62.9	59.7	62.5	63.0	59.4	52.1	0.98 (0.96-0.99)	0.009
51-99	2.9	6.4	7.5	7.0	8.0	8.0	7.6	6.7	7.7	6.3	1.01 (0.96-1.07)	0.685
≥ 100	33.0	22.7	26.4	26.6	29.1	32.3	29.9	30.3	32.9	41.5	1.04 (1.01-1.08)	0.014
Risk-adjusted												
RAS-antagonists (%)												
% of target dose												
≤50	46.8	47.2	44.9	48.6	45.0	42.7	47.5	46.8	46.2	40.6	1.00 (0.98-1.01)	0.647
51-99	6.3	7.6	7.1	8.2	7.6	7.1	7.1	7.2	8.1	11.2	1.02 (0.97-1.07)	0.390
≥ 100	46.8	45.2	48.2	42.7	47.4	50.3	45.0	46.0	44.8	47.9	1.00 (0.98-1.02)	0.925
Beta-blockers (%)												
% of target dose												
≤50	64.1	71.4	65.7	67.0	64.4	60.6	63.4	61.6	59.7	52.2	0.98 (0.96-0.99)	0.001
51-99	2.9	6.0	7.3	6.5	7.3	7.7	7.6	6.7	7.5	6.2	1.02 (0.96-1.08)	0.538
≥ 100	33.0	22.4	27.4	26.7	28.1	31.7	28.7	31.2	32.6	40.8	1.04 (1.01-1.07)	0.006

RAS, renin angiotensin system

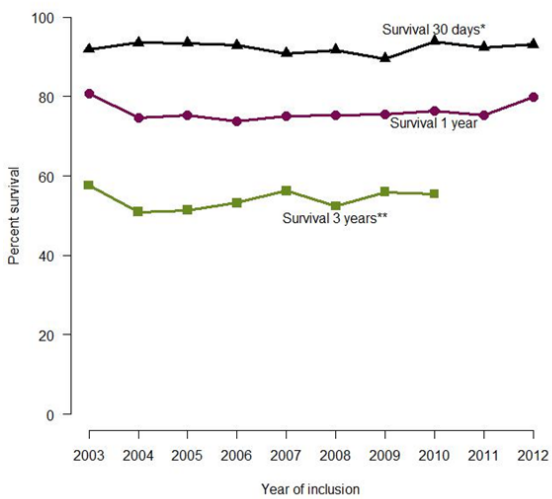

Figure 7. Crude survival over time.
*only for the hospitalized patients, **patients registered 2003-2010

Table 6. Risk-adjusted survival over time.
Sensitivity analysis I, Patients seen by cardiologist; Sensitivity analysis II, patients seen in internal medicine/geriatrics. *only for the hospitalized patients, **patients registered 2003-2010

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	RR per year (95% CI)	P for trend
30-day survival*												
Main study population	**91.8**	**93.7**	**93.7**	**92.6**	**90.0**	**90.9**	**89.4**	**92.4**	**91.4**	**93.6**	**1.00 (0.99-1.00)**	**0.532**
Sensitivity analysis I	88.6	92.2	95.8	94.6	89.8	90.3	88.0	89.4	89.1	90.9	0.99 (0.99-1.00)	0.033
Sensitivity analysis II	100.0	93.2	91.2	88.7	85.4	88.2	88.9	96.6	92.4	95.1	1.00 (1.00-1.01)	0.306
1-year survival												
Main study population	**80.8**	**77.5**	**79.3**	**75.3**	**75.2**	**75.6**	**75.9**	**76.1**	**75.2**	**76.9**	**1.00 (0.99-1.00)**	**0.260**
Sensitivity analysis I	83.5	80.8	78.9	80.9	75.0	77.2	75.3	74.5	77.1	75.7	0.99(0.99-1.00)	0.006
Sensitivity analysis II	75.0	70.7	75.8	65.3	71.2	69.7	73.0	73.4	69.4	75.2	1.00(0.99-1.02)	0.676
3-year survival**												
Main study population	**57.6**	**55.7**	**57.1**	**56.2**	**56.3**	**53.2**	**56.7**	**54.3**	**-**	**-**	**0.99 (0.98-1.01)**	**0.425**
Sensitivity analysis I	60.0	59.3	62.9	60.6	57.5	56.1	58.2	54.4	--	--	0.99(0.97-1.00)	0.067
Sensitivity analysis II	52.5	45.8	45.6	44.1	49.1	45.4	48.8	46.6	--	--	1.01(0.98-1.03)	0.623

Study II

The flow of registrations, validation process and selection of controls is shown in Figure 8. Inotrope use was confirmed in 655 registrations from 22 centers. In 618 of those, levosimendan was used (including 21 registrations with both levosimendan and conventional inotropes). Of all levosimendan registrations, 38% were planned repetitive treatment. We identified 4,418 inpatient controls in NYHA III-IV and EF<40%. Of registrations with confirmed levosimendan use, 2 were out-patient visits and 97 had either NYHA class I-II or EF ≥40% (in contrast to the controls). Selected numbers and percentages on registrations and reporting centers are shown in table 7 and indications for levosimendan treatment are depicted in Table 8. Patients who received planned repetitive levosimendan treatment (as opposed to acute treatment and controls) were younger, more commonly male, and more frequently treated in cardiology. They had better renal function and they had more evidence-based treatments (table 9). One-year survival was 81% for patients with planned repetitive levosimendan, 62% for patients with acute levosimendan and 66% for the controls, the survival curves are shown in Figure 9. Proportions of levosimendan treatment to total registrations and patients are shown in Figure 10. The proportion of treatment to total registrations ranged between 1 and 52% and the proportion of planned repetitive to total levosimendan registrations ranged between 0 and 65%. Of the 87 patients who received planned repetitive levosimendan, existing interventions were: CRT 41%, ICD 41%, HTx 1% and LVAD unknown (assumed 0%). Potential interventions among the remaining, not already treated were: CRT: 46%, ICD 98%, Htx 49% and LVAD 58%.

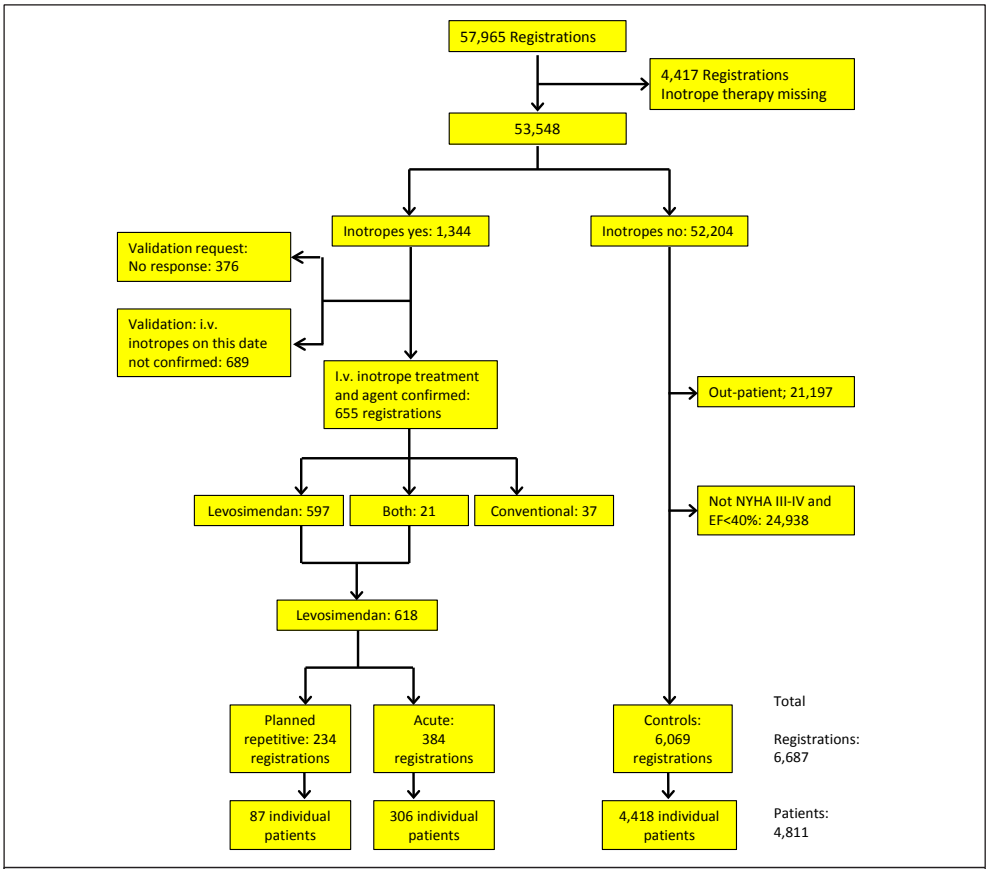

Figure 8. Flowchart of registrations, validation and individual patients.
NYHA, New York Heart Association; EF, ejection fraction

Table 7. Selected numbers and percentages
*Control registrations were in-patients

Number	n	Percentages	%
Registrations with ”received inotropes” = yes	1344	Percent of total registrations	2.5
Hospitals reporting ”received inotropes” = yes	54	Percent of total reporting hospitals	86
Hospitals responding and validating individual patient inotrope use	22	Percent of total reporting hospitals	35
Hospitals of these 22 that validated levosimendan use	21	Percent of total reporting hospitals	33
Iv inotropes use and agent confirmed at the relevant hospitalization	655	Percent of all in-patients with NYHA III-IV and EF <40%*	10
Levosimendan registrations	597	Percent of inotrope registrations	91
Acute levosimendan registrations	384	Percent of acute inotrope registrations	
Planned repetitive levosimendan registrations	234	Percent of levosimendan registrations	38
Planned repetitive levosimendan patients	87	Inotrope patients + controls	1.8
Planned repetitive levosimendan patients	87	Levosimendan patents	22

NYHA III-IV and EF <40%. NYHA, New York Heart Association; EF, ejection fraction

Table 8. Levosimendan indications.

Indication for levosimendan use	Registrations n (%)
Planned repetitive registrations	234 (38)
Acute	
• Acute decompensated heart failure	331 (54)
• Acute coronary syndrom	42 (7)
• Peri-operative	3 (0.5)
• Unknown indication	8 (1)

Table 9. Patient characteristics.

Variable	% missing	Planned repetitive levosimendan n=87 patients (1.8%)	Acute levosimendan n=306 patients (6.4%)	No inotropes (controls) n=4418 patients (92%)	P planned vs. acute	P planned vs. control	P acute vs. control
Follow-up time, days	0	627 (217-966)	372 (90-765)	494 (144-1008)			
Number of dead	0	30 (34%)	152 (50%)	2419 (55%)			
Demographics							
Age, years	0	64 (56-74)	69 (58-76)	78 (69-84)	0.074	<0.001	<0.001
Gender, male	0	79 (91%)	253 (83%)	3082 (70%)	0.067	<0.001	<0.001
Married / co-habitating	5	67 (79%)	178 (60%)	2293 (55%)	0.001	<0.001	0.091
Independent living	10	80 (100%)	253 (97%)	3694 (92%)	0.123	0.002	0.007
Cardiology specialty	0	82 (94%)	262 (86%)	2520 (57%)	0.041	<0.001	<0.001
Specialty follow-up	15	81 (98%)	220 (81%)	2064 (55%)	<0.001	<0.001	<0.001
Clinical							
NYHA at discharge	1				0.035	<0.001	<0.001
I		4 (5%)	5 (2%)	0 (0%)			
II		16 (21%)	37 (15%)	0 (0%)			
III		46 (61%)	141 (57%)	3717 (84%)			
IV		10 (13%)	65 (26%)	701 (16%)			
EF, %	0				0.078	<0.001	<0.001
≥ 50		0 (0%)	12 (4%)	0 (0%)			
40-49		3 (4%)	20 (7%)	0 (0%)			
30-39		20 (24%)	48 (16%)	1719 (39%)			
< 30		60 (72%)	219 (73%)	2699 (61%)			
Systolic blood pressure, mm Hg	1	105 (95-118)	107 (95-120)	120 (105-130)	0.911	<0.001	<0.001
Diastolic blood pressure, mm Hg	1	70 (60-70)	65 (60-72)	70 (60-80)	0.893	<0.001	<0.001
Heart rate, beats per minute	9	70 (68-77)	77 (70-90)	75 (67-86)	<0.001	0.019	0.002
Chest x-ray confirmed congestion	19	13 (24%)	116 (50%)	1953 (54%)	<0.001	<0.001	0.175
QRS ≥ 120 ms*	39	11 (46%)	64 (40%)	1235 (45%)			
Laboratory							
Creatinine clearance, ml/min	5	68 (46-91)	57 (39-89)	48 (33-70)	0.056	<0.001	<0.001
Hemoglobin, g/L	0	130 (116-142)	125 (114-139)	129 (117-142)	0.161	0.904	0.005
NT-pro-BNP, pg/mL	76	3839 (924-7650)	6830 (3130-15408)	6280 (3126-12866)	0.001	0.001	0.459
Medical history							
Hypertension	4	27 (32%)	101 (34%)	1909 (45%)	0.697	0.020	0.001
Diabetes mellitus	1	29 (33%)	98 (32%)	1361 (31%)	0.897	0.641	0.654
Ischemic heart disease	3	50 (57%)	179 (60%)	2632 (61%)	0.712	0.505	0.540
Atrial fibrillation/ flutter	1	45 (52%)	143 (47%)	2179 (50%)	0.466	0.746	0.344
Lung disease	3	11 (13%)	60 (20%)	852 (20%)	0.155	0.131	0.940

Table 9. Patient characteristics.

Variable	% missing	Planned repetitive levosimendan n=87 patients (1.8%)	Acute levosimendan n=306 patients (6.4%)	No inotropes (controls) n=4418 patients (92%)	P planned vs. acute	P planned vs. control	P acute vs. control
Medications							
ACE-inhibitor and/or ARB	2	80 (93%)	247 (82%)	3565 (82%)	0.011	0.009	0.755
B-blocker	0	83 (95%)	266 (87%)	3878 (88%)	0.032	0.029	0.649
MRA	0	58 (67%)	172 (57%)	1745 (40%)	0.108	<0.001	<0.001
Digoxin	0	26 (30%)	71 (23%)	885 (20%)	0.208	0.030	0.185
Diuretic	0	82 (94%)	281 (92%)	4067 (92%)	0.647	0.684	0.826
Oral anticoagulant	0	58 (67%)	162 (53%)	1623 (37%)	0.028	<0.001	<0.001
Existing alternative treatments							
CRT	1	35 (41%)	62 (20%)	248 (6%)	<0.001	<0.001	<0.001
ICD	1	35 (41%)	53 (17%)	232 (5%)	<0.001	<0.001	<0.001
Heart transplant	9	1 (1%)	1 (0%)	5 (0%)	0.416	0.111	0.313
LVAD	NA	NA	NA	NA	NA	NA	NA
Alternative treatment candidates#							
CRT candidate	40	11 (46%)	59 (37%)	1224 (45%)	0.501	1.000	0.058
ICD candidate	8	48 (98%)	218 (88%)	4154 (100%)	0.038	0.012	<0.001
Heart transplant candidate	10	37 (49%)	101 (40%)	718 (18%)	0.183	<0.001	<0.001
LVAD candidate	0	48 (58%)	171 (57%)	1256 (28%)	1.000	<0.001	<0.001

Data are median (interquartile range) or n (%)
p is by Mann-Whitney U or Fischer's exact test
*QRS width is assessed only in patients without pacemaker, CRT or ICD.
#Candidacy for alternative treatment was assessed on planned repetitive patients only and is explained in the text.
ACE-inhibitor, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRT, cardiac resynchronization therapy; EF, ejection fraction; ICD, implantable cardioverter defibrillator; LVAD, left ventricular assist device; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; NA, not applicable;
LVAD patients are cared for in surgical departments and not reported to the Registry and are rare in Sweden.

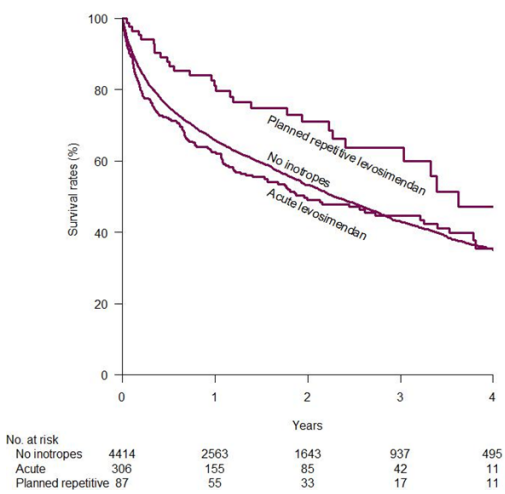

Figure 9. Crude descriptive survival by Kaplan-Meier analysis. No association between treatment and outcome is assessed.

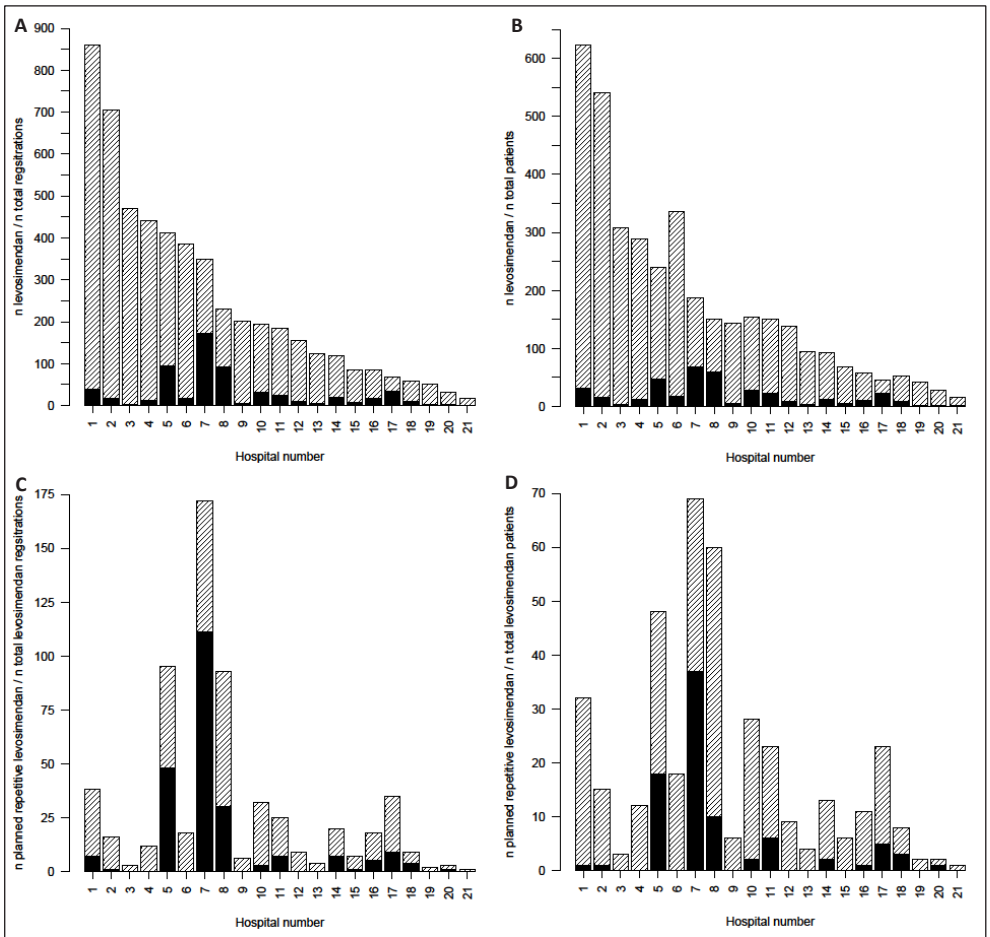

Figure 10. Use of levosimendan by individual hospitals: a) Number of levosimendan registrations (black) as a proportion of total registrations, b) Number of levosimendan individual patients (black) as a proportion of total individual patients, c) Number of planned repetitive levosimendan registrations (black) as a proportion of total levosimendan registrations, d) Number of planned repetitive levosimendan individual patients (black) as a proportion of total levosimendan individual patients

Study III

Patient selection is depicted in Figure 11. Included in the main analysis were 10,062 unique patients with EF <40% and NYHA class III-IV from SwedeHF between 2000 and 2013. The number of patients in age groups were as follows: 2,247 age ≤65 years, 4,632 age 66 to 80 years and 3,183 age >80 years. Younger patients were generally healthier and had more evidence-based treatment, they had lower EF and were more commonly male.

Overall one-year and five-year survival, observed vs. expected were 76 and 39% vs. 95 and 76% (Figure 12A). By age groups, the corresponding numbers were as follows: age ≤65 years, 90 and 68% observed vs. 99 and 96% expected (Figure 12B); age 66 to 80 years, 79

and 40% observed vs. 97 and 83% expected (Figure 12C); and age >80 years, 61 and 17% observed vs. 89 and 52% expected (Figure 12D). The relative difference between excess mortality and actual mortality was higher in the age groups up to 80 years compared to >80 years.

The predefined risk factors were all independent predictors of mortality (Table 10 and Figure 13). Figure 12 displays the hazard ratios for the five risk factors and the additional 12 selected variables. Survival by number of the five risk factors is shown in Figure 14a and Table 10. The presence of one risk factor was associated with a one-year survival of 79%. For comparison, one-year survival for HTx is around 90% and LVAD around 80%. Survival decreased progressively by number of risk factors. A separate analysis on NYHA class II is shown in Table 11 and Figure 14b. The survival by risk factors was higher compared to NYHA III-IV.

The c-index for the 5-risk factor-model was 0.71, and the c-index for the one-variable-model on cumulative number of risk factors was 0.73.

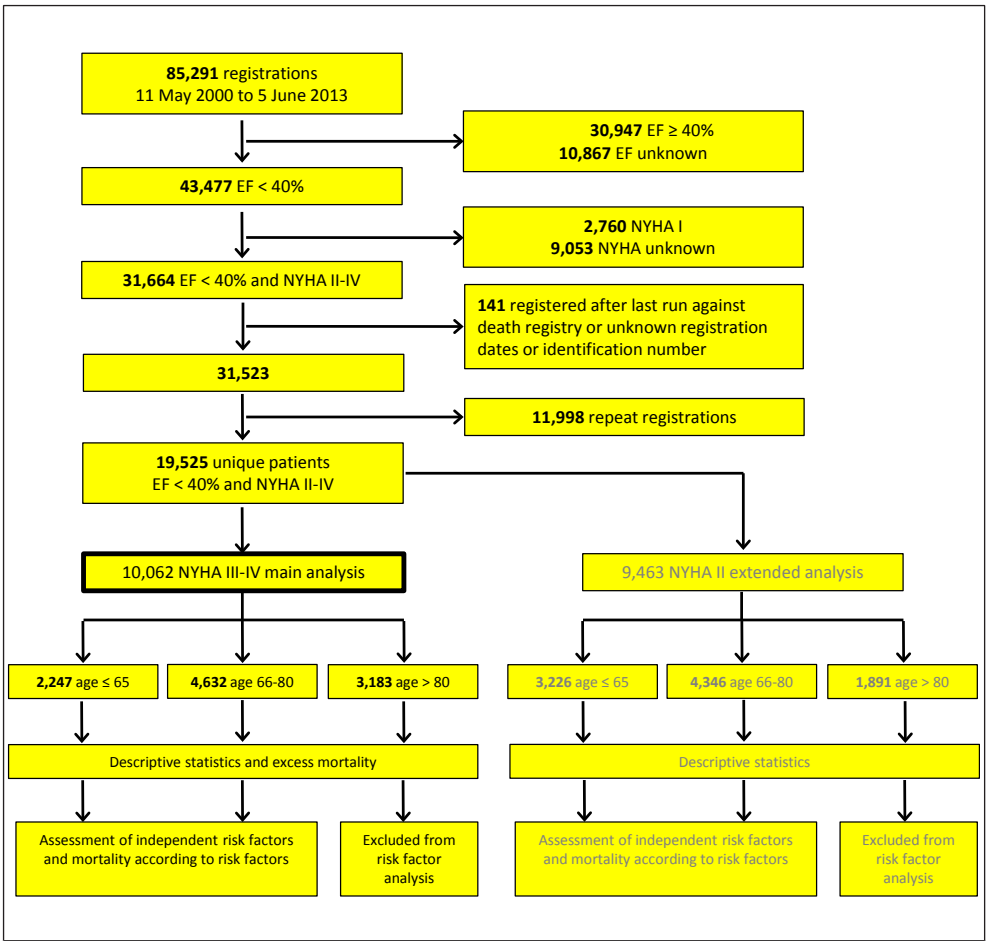

Figure 11. Patient selection.

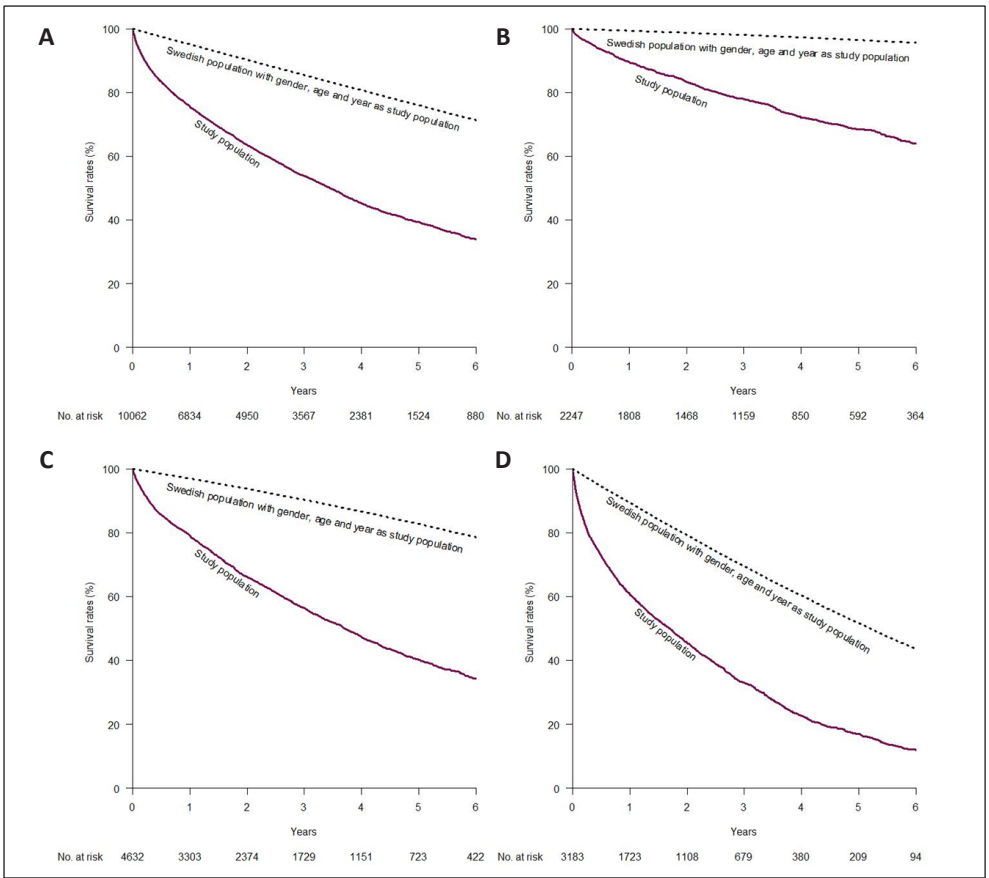

Figure 12. Observed and expected all-cause mortality, NYHA class III-IV
a) overall, b) age ≤65 years, c) 66-80 years, d) >80 years.
NYHA, New York Heart Association

Table 10. Survival by a) each of the 5 risk factors and b) the cumulative number of risk factors. Patient <80 years, NYHA class III-IV

A. Risk factor* Reference level for HR	n dead / n total	1-year survival	HR	95% CI	p-value
Systolic BP ≤ 90 mm Hg	304/520	68%	1.64	1.43-1.88	<0.001
Systolic BP > 90 mm Hg	2673/6359	84%			
Creatinine ≥ 160 µmol/L	611/827	58%	1.91	1.72-2.12	<0.001
Creatinine < 160 µmol/L	2366/6052	86%			
Hemoglobin ≤ 120 g/L	929/1568	69%	1.32	1.21-1.43	< 0.001
Hemoglobin > 120 g/L	2048/5311	86%			
Not treated with RAS-antagonist	401/559	58%	1.56	1.39-1.75	<0.001
Treated with RAS-antagonist	2576/6320	85%			
Not treated with β-blocker	352/587	71%	1.28	1.14-1.44	<0.001
Treated with β-blocker	2625/6292	84%			
B. Number of risk factors†	**n dead / n total**	**1-year survival**	**HR‡**	**95% CI**	**p-value**
0	1262/3905	90%			
1	944/1870	79%	1.40	1.28-1.53	<0.001
2	488/672	60%	2.30	2.05-2.57	<0.001
3-5	186/221	39%	4.07	3.44-4.82	<0.001

NYHA, New York Heart Association; HR, hazard ratio; BP, blood pressure; RAS renin angiotensin system

Table 11. Survival by a) each of the 5 risk factors and b) the cumulative number of risk factors. Patient <80 years, NYHA class II

A. Risk factor* Reference level for HR	n dead / n total	1-year survival	HR	95% CI	p-value
Systolic BP ≤ 90 mm Hg Systolic BP > 90 mm Hg	69/268 1630/7304	91% 94%	1.10	0.85-1.43	0.477
Creatinine ≥ 160 µmol/L Creatinine < 160 µmol/L	183/354 1516/7218	79% 95%	1.74	1.46-2.07	<0.001
Hemoglobin ≤ 120 g/L Hemoglobin > 120 g/L	385/1043 1314/6529	87% 95%	1.37	1.21-1.55	< 0.001
Not treated with RAS-antagonist Treated with RAS-antagonist	126/293 1573/7279	84% 94%	1.28	1.05-1.55	0.014
Not treated with β-blocker Treated with β-blocker	138/487 1561/7085	93% 94%	1.16	0.97-1.39	0.113
B. Number of risk factors†	**n dead / n total**	**1-year survival**	**HR‡**	**95% CI**	**p-value**
0	1005/5457	96%			
1	474/1566	91%	1.36	1.21-1.53	<0.001
2	142/317	84%	1.81	1.50-2.18	<0.001
3-5	37/57	66%	2.64	1.84-3.77	<0.001

NYHA, New York Heart Association; HR, hazard ratio; BP, blood pressure; RAS renin angiotensin system

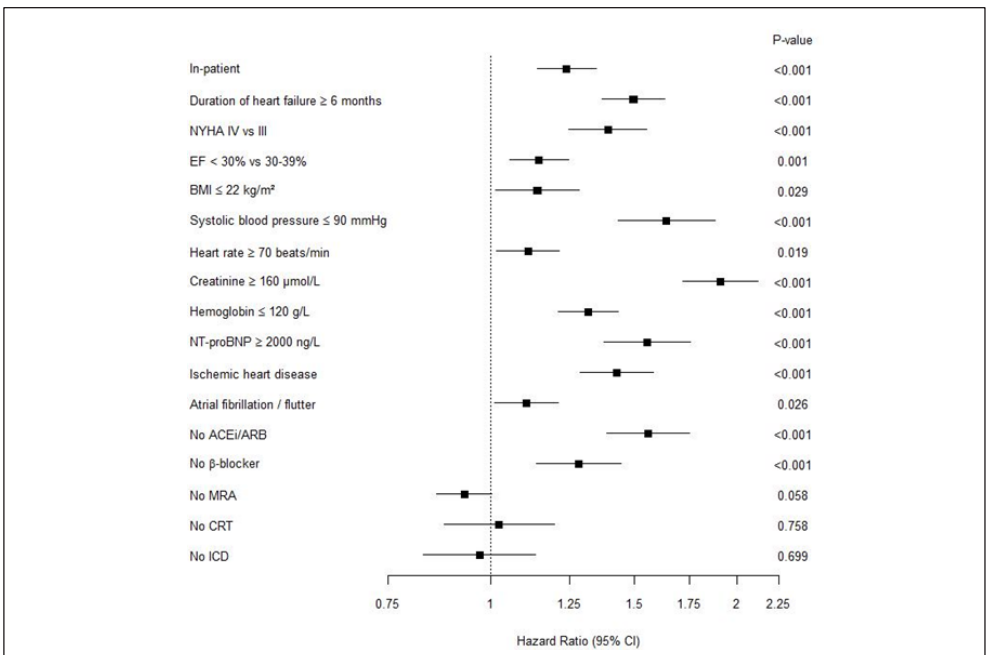

Figure 13. All cause mortality: Hazard ratios and 95% confidence intervals for the 5 main and 12 additional risk factors.

NYHA, New York Heart Association; EF, ejection fraction; BMI, body mass index; NT-proBNP, n-terminal probrain natriuretic peptide; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator.

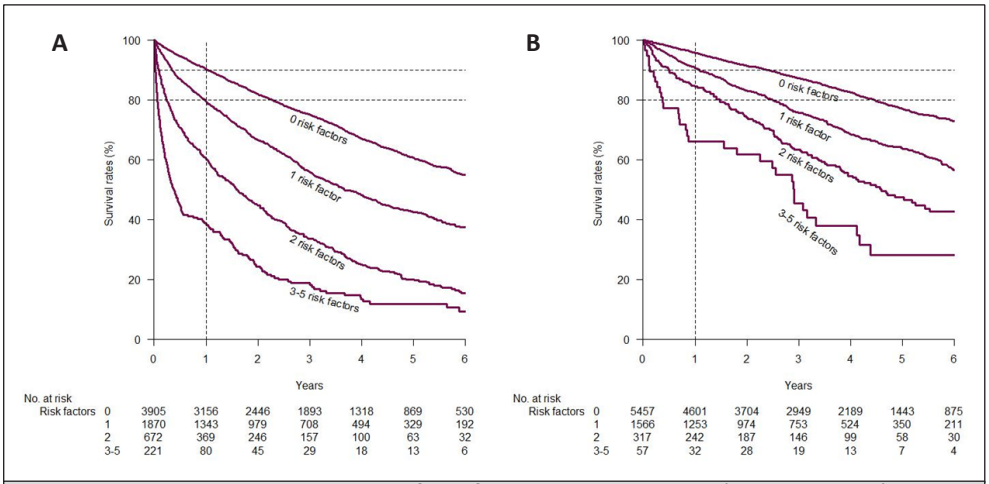

Figure 14. Survival rates by number of risk factors, age <80 years a) NYHA III-IV, b) NYHA II For comparison, dotted lines represent the approximate one-year survival for heart transplantation (90%) and left ventricular device (80%). The 5 risk factors were systolic blood pressure <90 mmHg, creatinine >160µmol/l, hemoglobin ≤120 g/l, no treatment with renin angiotensin system antagonist, no treatment with beta-blocker.

Study IV

Figure 15 illustrates the selection process of the HFpEF hospitalizations in the ARIC Surveillance. A sample of 2,304 (weighted sample of 10,789) hospitalizations were included for analysis. Overall, mean (standard error) age was 77 (0.27), 74% were white and 35% were male. Sixty-five percent had a prior diagnosis of HF and 29% had a prior hospitalization for HF. Twenty-eight-day and one-year mortality was 11 and 34% respectively. Those who died were older and more likely to be white. They were also more likely to be underweight and have a history of atrial fibrillation/flutter, anemia, pulmonary hypertension and valvular heart disease. Furthermore, those who died had higher levels of natriuretic peptides and blood urea nitrogen (BUN), lower levels of hemoglobin, and their BP at admission was lower.

Nine and 8 predictors of 28-day and one-year mortality respectively were identified (Figure 16a and b). The most powerful predictors in both models were higher patient age, higher BUN, hypoxia and lower hemoglobin levels. Discrimination measured by AUC was 0.774 and 0.724 for 28-day and one-year mortality respectively. Calibration was good, with non-significant Hosmer-Lemeshow p-values in both models.

The risk scores are shown in Table 12. The predicted mortality at 28 days and one year using the risk scores was 10 and 33% respectively yielding observed to predicted ratios of 1.10 and 1.03. The AUC for the short- and intermediate-term risk scores were 0.768 and 0.718 respectively. The distribution of the risk scores and association with mortality is shown in Figure 17 and calibrations plots are shown in Figure 18.

In the validation sample, 28-day and one-year mortality was 8 and 33% respectively. Distribution of the risk scores in the validation sample are shown in Figure 19. Discrimination in the validation sample was somewhat weaker than in the derivation sample. AUC was 0.700 and 0.692 for 28-day and one-year mortality respectively. Calibration was good as shown in Figure 20.

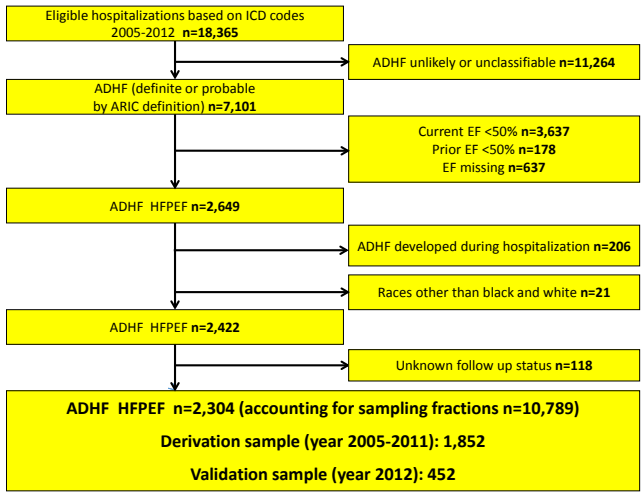

Figure 15. Selection of hospitalizations of HFpEF.
ICD, international classification of disease, ADHF, acute decompensated heart failure; ARIC, atherosclerosis risk in the commuity; EF,ejection fraction.

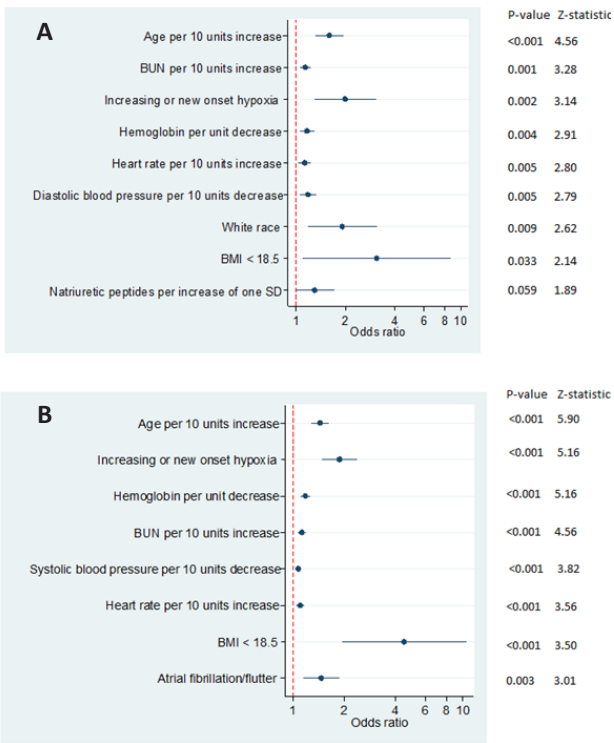

Figure 16. Predictors of a) 28-day and b) one-year mortality.
BUN, blood urea nitrogen; BMI, body mass index; SD, standard deviation
Hypoxia defined as documented saturation <90% or the word "hypoxia" stated in the medical records.

Table 12. Risk score

Predictor	**Points 28-day mortality**					**Max score**
Age	<70	70-80	≥80			
	+0	**+6**	**+10**			**+10**
BUN (mg/dL)	<30	30-70	70-110	≥110		
	+0	**+1**	**+8**	**+16**		**+16**
Hemoglobin (g/dL)	>13	11-13	9-11	<9		
	+0	**+4**	**+7**	**+10**		**+10**
Heart rate (bpm)	<70	70-90	90-110	110		
	+0	**+3**	**+5**	**+8**		**+8**
Natriuretic peptides						
BNP(pg/mL)	<196	196-1,642	≥1,642			
NT-proBNP age<75 (pg/mL)	<885	885-12,161	≥12,161			
NT-proBNP age>75 (pg/mL)	<1372	1372-13,884	≥13,884			
	+0	**+6**	**+13**			**+13**
Diastolic BP (mmHg)	≥100	70-100	<70			
	+0	**+6**	**+12**			**+12**
Hypoxia					**+7**	**+7**
White race					**+7**	**+7**
BMI <18.5 (kg/m²)					**+13**	**+13**
	Highest possible score					**91**
	Points one-year mortality					
Age	<70	70-80	≥80			
	+0	**+4**	**+8**			**+8**
Hemoglobin (g/dL)	>13	11-13	9-11	<9		
	+0	**+1**	**+6**	**+10**		**+10**
BUN (mg/dL)	<30	30-70	70-110	≥110		
	+0	**+2**	**+7**	**+10**		**+10**
Systolic BP (mmHg)	≥150	130-150	110-130	110		
	+0	**+3**	**+5**	**+6**		**+6**
Heart rate (bpm)	<70	70-90	90-110	>110		
	+0	**+4**	**+6**	**+7**		**+7**
Hypoxia					**+6**	**+6**
BMI <18.5 (kg/m²)					**+15**	**+15**
Atrial fibrillation/flutter					**+4**	**+4**
	Highest possible score					**66**

BUN, blood urea nitrogen; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; BP, blood pressure; BMI, body mass index;

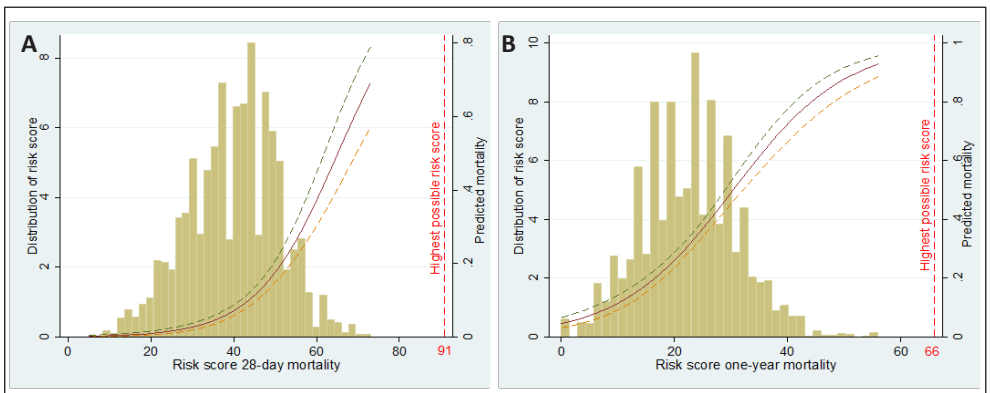

Figure 17. Distribution of risk score for a) 28-day and b) one-year mortality and the association with predicted mortality.

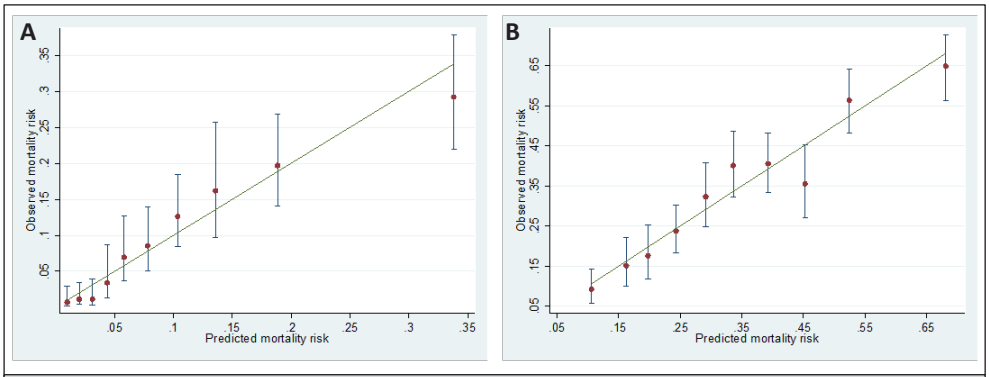

Figure 18. Observed vs. predicted mortality by deciles of risk score for a) 28-day and b) for one-year mortality

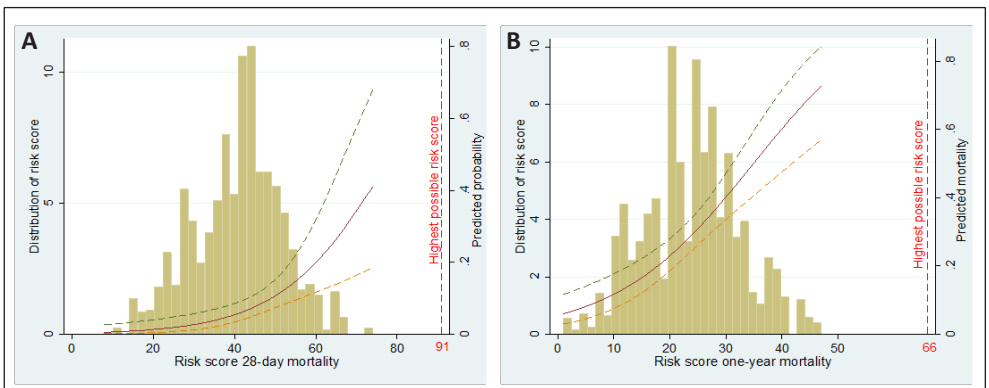

Figure 19. Validation: Distribution of risk score for a) 28-day and b) one-year mortality and the association with predicted mortality

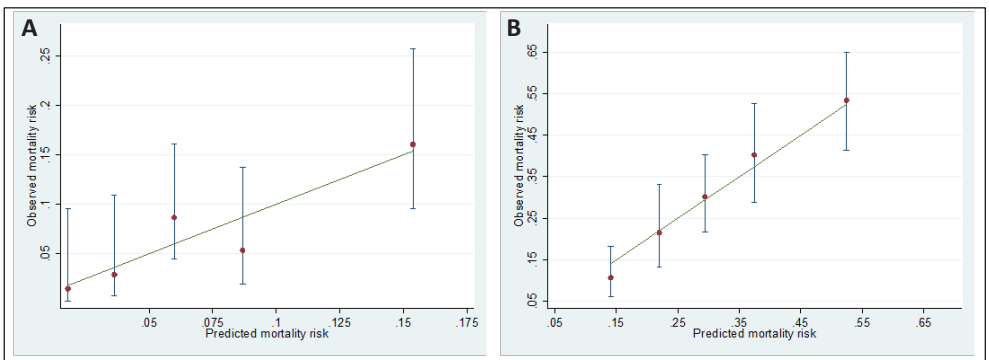

Figure 20. Validation: Observed vs. predicted mortality by deciles of risk score for a) 28-day and b) for one-year mortality

GENERAL DISCUSSION

Despite advancement in therapy for HFrEF, mortality remains high and the utilization of available treatment is unclear. HFpEF is still an unsolved dilemma with substantial uncertainties regarding disease phenotypes, prognosticators and treatment.

The first studies in the present thesis focus on contemporary prognosis, current treatment patterns and indications for referral for advanced therapy in HFrEF. (**Study I-III**). In the last part of the thesis mortality and prognosticators of HFpEF are studied (**Study IV)**.

Survival in heart failure

Substantial improvement in HF survival has been described before the turn of the millennium. In the Framingham study mortality improved by 12% per decade between 1950 and 2000 to about 10% at 30 days and 30% at one year[90]. Still, prognosis remains poor in HF and survival rates may have stagnated after the millennium. In **Study I**, one- and three-year survival of patients in NYHA class II-IV was around 80 and 55% respectively. There were no significant changes over time between 2003 and 2012. The lack of improvement in survival over time was probably related to the absence of increased utilization of existing and emerging treatments during the period. Our findings on survival were recently confirmed in a large HF cohort in general practice in the UK. A lack of improved survival was reported between 1998 and 2012 and one-year survival was 81%[91]. In **Study II and III** with mainly patients in NYHA class III-IV, one-year mortality ranged from 61-81% depending on age and severity of disease. In **Study II** patients who received repetitive levosimendan treatment had higher survival rates than controls. It is emphasized however, that these were crude numbers without any adjustments, and the difference is likely due to selection bias and not treatment effect. The relative survival analysis in **Study III** indicates that in patients below 80 years of age, mortality was mainly related to HF and/or HF associated comorbidities.

HFpEF is believed to have slightly better survival than HFrEF[19]. In **Study IV**, 28- day and one-year mortality in hospitalized HFpEF was 11 and 34%, respectively. These findings are consistent with some studies on ADHF[92,93], but higher than in others[94]. The relatively unselected and elderly population and high comorbidity burden in our data may partly explain the high mortality in our study.

Drug and device therapy in HFrEF

Pharmacological treatment with beta-blockers, RAS antagonists and MRA improve survival in HFrEF and strong recommendations from international guidelines support the use of these therapies in HFrEF[4,95]. The main findings in **Study I** were that the use of RAS antagonists and beta-blockers in Sweden was high and stable over time. The use of MRA decreased significantly from 53 to 42% risk-adjusted. Of note is that until the EMPHASIS-HF trial[40] was published in 2011, MRA was indicated only in NYHA III-IV and 29 to 37% of the patients in our study were in NYHA class II. The use of device therapy was overall poor despite a trend towards increased implementation over a 10-year period. Considering that the study population had EF<30%, a duration of HF > 6 months, and >50% had QRS prolongation (≥120ms), the use of CRT and ICD was markedly below expected and appropriate.

Underutilization of treatments

Other registries and even active programs to improve implementation of evidence-based treatments also report underuse of MRA ranging from 36% to 60% among patients with appropriate indication[96,97]. Non-treatment may partly be explained by be intolerance and frequent MRA-related side effects. We found that 30% discontinued MRA treatment between first and last visit. After the publication of RALES, a Canadian analysis reported an increase hyperkalemia-related complications[98]. However, these findings were not confirmed in a longitudinal cohort analysis from Scotland where increased laboratory monitoring of the patients was observed parallel to increased prescription of MRA [99]. This may indicate that severe side-effects can be minimized with proper monitoring and follow up. This may also be the reason why HF clinics appear to have similar rates of hyperkalemia to those observed in randomized trials[100].

Underutilization of device therapy has been reported previously[101-103]. Poor awareness and low referral rates amongst physicians are believed to be important causes of ICD underutilization[104,105]. A Swedish study from 2014 found this to be true both for ICD and CRT treatment[106]. The authors invited a random sample of Swedish physicians working in cardiology, internal medicine or family medicine, to fill in a survey on indications for device pharmaceutical therapy. Acceptable awareness was met by 32% for CRT and 15% for ICD treatment, and 37% stated that ICD is never indicated unless there is documentation of ventricular arrhythmias. Being a certified specialist in cardiology was the only significant predictor of reasonable awareness. In **Study I** we found a somewhat higher use of device therapy in patients seen by cardiologists and in centers that implant CRT and ICDs. LBBB is shown to be a predictor of mortality regardless of age and is more common with increasing age[107]. Additionally, in contrast to ICD, CRT treatment may be indicated for symptom relief, not only to improve prognosis[4]. Despite this, underutilization of CRT is more pronounced in the elderly[107].

In contrast to unawareness of guideline recommendations, reasons for low implementation may also be due to lack of convincing evidence. Even though prophylactic ICD therapy has a class I indication in the guidelines, the evidence behind ICD treatment is not as robust as for drug therapy. There is a controversy about survival benefits in the elderly since they are often excluded from randomized trials[108]. The survival benefit for non-ischemic HF also remains debated. The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) is the only randomized trial including non-ischemic cardiomyopathy to show a survival benefit. A positive effect was only seen in the NYHA class II (not III) and no patients were treated with CRT[50]. The very recent Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure (DANISH) study from 2016, thus not affecting the interpretation of the results at time of publication of **Study I**, randomized 1,116 patients with non-ischemic HF to receive ICD or conventional therapy. The association with the primary endpoint of all-cause mortality was not significantly different between the groups[52]. The current study differed from previous trials in the comprehensive HF drug treatment and the 58% concomitant CRT therapy. These treatments collectively reduce mortality substantially and thus make it harder to prove an additional effect on all-cause mortality from ICD treatment, especially since the risk of non-sudden and non-cardiovascular death increases with time[109]. In subgroup analysis, there was a significant survival benefit in the ICD arm for patients younger than 68 years of age. The implications of this study on future guidelines and treatment patterns is still unclear.

Treatment of HF in the elderly remains a challenge. They have a high comorbidity burden,

treatment is complicated by multipharmacy and frailty. Furthermore, few randomized trials have focused on quality of life, a parameter that may have a higher priority in these patients than reduction in mortality. The elderly are also underrepresented in clinical trials, mean age in the large randomized HF trials that treatment guidelines are based upon is just over 60 years and less than 30% of the participants are older than 70 years[110]. Registry based, real world data however, indicate reduction in mortality and hospitalization rates for guideline recommended evidence-based treatments even in the elderly[111,112]. Moreover, in **Study III** we showed that up to 80 years of age mortality in HFrEF patients was mainly HF related. Cognitive function, frailty and patient preference are important elements in the decision-making in HF management in the elderly. These factors, commonly not captured in studies, may partly explain the underuse of HF treatments in our studies. Furthermore, it may be assumed that older patients with chronic disease prefer improved symptoms to prolonged survival. However, a study of end-of-life preferences in HF showed that the majority of the patients preferred longevity over quality of life and that prediction of preference was inaccurate[113]. Patient-centered management including an open dialogue about expectations, preferences and available treatments is important to provide optimal care in the elderly.

Levosimendan in heart failure

Inotropic drugs are used to stabilize patients with ADHF with compromised systemic perfusion and end-organ function. Evidence is conflicting, and treatment with inotropic agents has even been reported to be harmful[73-75]. In **Study II** the relatively novel inotrope levosimendan was found to be the most frequently used inotrope in cardiology and internal medicine in Sweden. At least 10% of hospitalizations with NYHA III-IV and EF<40% received inotropes, a surprisingly high number considering that only 4% of ADHF have cardiogenic shock[8]. A possible explanation for this is the extensive use of planned repetitive levosimendan treatment, 38% of all levosimendan registrations, that we report. It is interesting that this type of levosimendan treatment in the non-acute setting has become established in some hospitals in Sweden, despite the lack of convincing evidence. Possible explanations may be increasing patient demand or the physician's wish to "do something" for a patient when no further treatment options exists, as well as a bridging strategy to maintain organ function while awaiting HTx. We found however, that 59% of the patients who received planned repetitive levosimendan did not have device therapy. Of these, 46 and 98% had indications for CRT and ICD respectively. To justify a treatment with limited evidence, prior optimization of guideline-recommended, evidence-based treatment should be performed.

Referral to a heart failure center for potential advanced therapy

With progression of disease and symptoms despite optimal medical and device therapy, possible interventions are advanced therapies such as HTx and LVAD. Patients are however believed to be underserved with these treatments[16,60]. Organ shortage is limiting the number of possible HTx, whereas the reasons for underutilization of LVADs are unclear. Possible explanations include physician and patient skepticism and doubts regarding cost effectiveness and medical benefits, but the major reason is however most likely unawareness. For general practitioners or cardiologists who do not deal with advanced HF on a daily basis, it may be difficult to identify patients who may benefit from HTx or LVAD therapy. Furthermore, the speed of disease progression in HF is often unpredictable and optimal timing for potential LVAD implantation is hard to define[16]. Patients are often referred too late, when end-organ

failure that disqualify for treatment is already present[16]. Valuable prognostic tools in the patient selection process such as peak VO_2, HFSS and SHFM are likely too complex for general practitioners[16,62]. In **Study III**, we propose that the comprehensive assessment of indications and contraindications for HTx and LVAD therapy should be performed in HF centers were knowledge and experience in this field is high. We introduce five simple risk factors and propose that the presence of at least one of these should prompt referral to a HF specialist. The five risk factors are systolic BP ≤90 mm Hg; creatinine ≤160 mmol/L; hemoglobin ≤120 g/L; no RAS antagonist; and no beta-blocker. These factors were prospectively selected because of their ability to independently predict mortality (based on previous literature, but confirmed in our data), and their simplicity and availability in daily practice. Additionally, when one or more of these risk factors become present, they reflect a change in the progression of disease and a change in prognosis, as opposed to risk factors such as ischemic etiology or sex. In patients <80 years of age, the presence of one risk factor indicate worse one-year survival than post HTx and post LVAD implantation[114].

What would the impact of these referral criteria be? In our study, 41% of the patients <80 years of age fulfilled the proposed criteria for referral to a HF specialist. A referral for evaluation, by no means equals HTx or LVAD indication. As outlined above, the selection process is complex, and detailed assessment of indication, contraindications, patient preference and motivation needs to be performed to identify patients suitable for treatment. Furthermore, before referral for advanced therapy, patients should have optimal evidence-based drug and device treatment. Both in **Study I** and **Study II** utilization of ICD and CRT was poor. If a patient does not receive guideline recommended treatment, evaluation by a HF specialist for optimization seems motivated. Intolerance to beta-blockers and RAS-antagonists has repeatedly been shown to be a marker of poor prognosis in HF[27]. Whether the absence of treatment in our data is due to true intolerance or more reflects the treating physician's perception of contraindications or limited monitoring possibilities is unclear. Regardless, both of these reasons motivate referral to a HF specialist. With the proposed referral criteria, many of the patients will be too sick and beyond possible advanced treatment options, especially those with several risk factors present. Apart from a high risk of death and frequent hospitalization admissions, these patients experience marked reduction in quality of life, and depression and anxiety is common[115]. A randomized controlled trial recently published showed that palliative programs can reduce readmissions and improve symptoms in patients with end stage HF (ESHF)[116]. Palliative care is substantially less implemented in HF than in cancer, and it is often initiated too late[117,118]. A HF specialist may be better suited in identifying patients with ESHF than generalists, hence even for this patient group referral to a HF center is justified.

HFpEF

The discussion of utilization of evidence-based treatments is limited to half of the HF population. For the other half, the patients with HFpEF, no evidence-based treatment is available. HFpEF remains a huge clinical challenge, and the prevalence is thought to be increasing with the aging population. In the search for treatments and treatment targets, a better understanding of the HFpEF population is needed. Furthermore, despite the absence of treatment options, it is still valuable to assess prognosis and identify high-risk patients in need for intensified in-hospital and early post-discharge monitoring. In **Study IV** predictors of 28-day and one-year mortality were identified in patients hospitalized with ADHF and

preserved EF and a score for risk evaluation at hospital admission was created. Most identified predictors in our study confirmed findings from previous studies on ADHF regardless of EF[119-121]. Symptoms and signs as risk predictors are however, mostly not assessed in risk models. We found hypoxia at admission to be one of the four most powerful predictors of both short and intermediate-term mortality. To our knowledge this has not been described previously. Both low[122] and high[123] systolic BP have been found to be predictors of mortality in acute decompensated HFpEF. It has been hypothesized that patients presenting with ADHF and high BP vs. low BP differ in characteristics and possibly underlying pathophysiology. Those with high BP may be in early or mid-stage of the disease, and those with low BP in more advanced low output stage of the disease[124] or with more severely impaired systolic contractility despite preserved EF. In HFpEF, hypertrophy, a small left ventricle and high filling pressures may contribute to a low output state[122]. We found lower systolic BP to be a predictor of one-year mortality and lower diastolic BP to be a predictor for 28-day mortality. The reason for this difference is unclear. In previous studies, diastolic BP has been a weaker predictor than systolic BP in acute settings[124].

Risk score

Numerous risk scores have been developed for risk prediction and estimation of prognosis in HF out of which some have gained an important role in clinical decision-making, e. g. SHFM and HFSS for transplantation selection[26,27]. Important performance measures of a risk score include discrimination, i. e. the ability to separate those with and those without an outcome of interest, and calibration, i. e. how well predicted outcomes match observed outcomes. Furthermore, to prove the risk score's generalizability, its performance should be validated in a different dataset from which it was derived. Our risk scores had good discrimination assessed by AUC and calibration assessed by Hosmer-Lemeshow statistics and plots of predicted vs. observed mortality. We performed validation of the risk scores in the latest addition to the dataset of hospitalizations from 2012, however, an important next step will be validation in a different cohort. A goal for the risk scores in **Study IV** was to use variables available in daily practice and to keep the scores as simple as possible. Hence, in the model building we removed variables despite statistical significance if their contribution to discrimination of the model was negligible. We ended up with 9 and 8 variables respectively in the risk scores for short- and intermediate-term mortality. A next step to facilitate the use of the risk scores will be to create a web-based calculator.

Ideally, a risk score should have some impact on treatment. We created a risk score for a population of patients were no evidence-based treatments exists. Risk prediction may still be of use to guide decisions regarding in-patient and early post-discharge care and to help patients and family to a better understanding of disease severity. Furthermore, a potential use may be in trial design for patient selection in ADHF and HFpEF.

Strengths and limitations of the datasets

Data in **Study I-III** are from SwedeHF, one of the world's largest HF registries with more than 70,000 patients in total and around 9,000 patients registered annually. Since the registry was founded an increasing number of sites report to the registry and an increasing number of patients are registered annually. The registry is representative for HF hospital care in Sweden, given that 19 out of 21 counties and more than 60 of about 75 hospitals,

including both university hospitals and community hospitals, are represented in the registry. Possibly, participating centers as opposed to non-participating centers, are biased towards more academic interest and more HF focused cardiology departments, resulting in a more ambitious HF care. Capture of primary care centers is poor with only 10% of primary care centers reporting to the registry.

In **Study II,** we performed a validation of the "inotrope" variable in the registry. Of the registrations with inotropes "yes" that were validated, only 68% were confirmed with inotrope use (Figure 6, **Study II**). The 32% not-confirmed inotrope use were in the validation found to be incorrect recordings or patients had received other drugs that may have been interpreted as inotropes, e.g. digoxin. The Registry performs validation on selected variables at randomly chosen centers every year. The 32% of incorrect registrations that we found is a much higher number that what has been found for other variables. Reasons for this may be that inotropes are often administered in the intensive care unit (ICU). The nurses that performed the validation may not have had access to ICU medical charts. Hence, inotropes were likely administered in many cases rather than incorrectly registered, but not confirmed in the medical records. Furthermore, validation was complicated by the fact that registrations went back to 2000, a time were drug treatment was not electronically documented.

In the community surveillance of the ARIC study (**Study IV**), medical records are abstracted by trained staff and hospitalizations are adjudicated as ADHF. The adjudication has been shown to have a higher sensitivity than simply using un-validated HF discharge codes in identifying ADHF hospitalizations[125]. The use of a stratified randomized sampling technique for the selection of hospitalizations and the participation of four diverse United States Communities in the Surveillance lead to generalizable and external valid findings.

A limitation of the Surveillance is that unique patients cannot be identified. Analysis is based on hospitalizations and patients that are rehospitalized may reoccur in the dataset. However, with the use of sampling criteria for selection of hospitalizations, this possibility is minimized. With a mean sampling fraction of 0,213 and a prior hospitalization for HF documented in around 30% and not necessarily in the study period, a maximum of 6% of the hospitalizations could represent rehospitalizations of patients already captured in the dataset.

Future perspectives

As outlined above, the underutilization of evidence-based therapies seen in our studies seems to be a universal problem in the care for HF patients. Parallel to the search of novel treatments, existing evidence-based treatments must be implemented. New strategies are needed to increase awareness and reduce the gap between guideline-recommended therapy and actual provided therapy in clinical practice. Active programs and care initiatives such as "Get with the Guidelines" and the "Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Out-patient Setting" (IMPROVE-IT) have led to improvements in care[91,126]. In the IMPROVE-IT program, specific patient-level performance feedback to the treating cardiologist appeared to be of particular importance in order to improve conformity with guideline recommendations. SwedeHF has so far been only descriptive, without specific quality improvement mechanisms. Introduction of more quality controls and feedback from the registry to care givers would extend the scope of the registry and might motivate more centers to participate. The use of screening programs to identify patients for device therapy and advanced HF treatment may be effective and should be evaluated further[64]. A future

project, as a follow-up to **Study III**, would be to evaluate the use of the proposed criteria for referral to a HF specialist and the potential effect on utilization of treatments and identification of patients for advanced therapy. Although it would be desirable, it is currently not feasable to treat all HF patients in cardiology units. In Sweden, around half of the HF patients are followed mainly in primary care[127]. Better collaboration and shared care between the primary care physician and the cardiologist are needed.

An aging population is well described in population demographic trends. More studies and evidence on HFrEF treatments in the elderly are warranted. With HFpEF being a disease of the elderly, prevalence will continue to increase. Studies must continue to characterize the HFpEF population and its phenotypes. With the heterogeneity of HFpEF, characterization of subgroups and identification of representative populations seem crucial in the search for new treatment options.

CONCLUSIONS

1) Mortality in HFrEF in Sweden remains high and has not changed over time. Evidence-based treatment is underutilized in Sweden, in particular the use of device therapy.

2) Levosimendan is the dominant choice of inotrope in cardiology and internal medicine in Sweden. Effects of the frequent use of planned repetitive levosimendan treatment in a non-acute setting needs to be evaluated further.

3) In patients with moderate to advanced HF, up to 80 years old, mortality is mainly related to HF and HF associated comorbidities. The use of few and simple risk factors as referral criteria to a HF center may increase the number of patients who can benefit from advanced therapies.

4) Age, BUN, hypoxia and low hemoglobin are strong predictors for 28-day and one-year mortality in patients hospitalized with acute HFpEF. The novel risk scores can provide estimates for mortality in these patients.

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